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MEDICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 13, 2011

From: Kathy M. Robie Suh, M.D., Ph.D.
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Division of Hematology Drug Products (HFD-160)

Subject: Medical Team Leader Secondary Clinical Review
NDA 22-406 resubmission, letter date 1/14/2011; received 1/14/2011
XARELTO^{R} (rivaroxaban) for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery

To: NDA 22-406

Xarelto (rivaroxaban) Tablets is an orally administered Factor Xa inhibitor being developed for several anticoagulation indications. In this NDA application the sponsor is seeking initial marketing approval of rivaroxaban for the indication: for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. The proposed dose is 10 mg orally once daily with a treatment duration of 14 days for knee surgery and 35 days for hip surgery.

This is the second review cycle for this drug product. See my Medical Team Leader/CDTL review dated 5/27/2009 for background and summary of cycle 1 review findings. Briefly, the database consisted of four trials (the RECORD 1, 2, 3, and 4 studies), each comparing rivaroxaban to enoxaparin (different regimens) with two studies for knee surgery and two studies for hip surgery. All four studies were multinational, randomized (1:1), double-blind, double-dummy, parallel groups design. The studies were conducted by Bayer but the right of reference for use of the studies was transferred to Johnson & Johnson (J & J) just prior to NDA submission and J & J is the sponsor of the NDA.

The first review cycle found convincing statistical evidence for efficacy of rivaroxaban in the two proposed clinical settings based on the primary efficacy endpoint total VTE (composite of any DVT [venographically determined], non-fatal PE or death) and concluded that, barring gross irregularities in conduct of the RECORD studies, rivaroxaban has efficacy as an anticoagulant for thromboprophylaxis in the settings of elective hip replacement and knee replacement surgery. The predominant effect appeared to be on venographically-detected DVT. The safety data suggested that bleeding rates may be somewhat greater with rivaroxaban than with enoxaparin. Though the available data did not identify a risk for hepatotoxicity, most of these data were from short-term studies and insufficient data were available to rule out a risk for hepatotoxicity with

longer term use of rivaroxaban. Chronic use is a concern for rivaroxaban, since as an oral agent it can be reasonably expected to have some long-term use in practice for treatment of chronic indications, such as stroke prevention in patients with atrial fibrillation. A meeting of the Cardiovascular and Renal Drugs Advisory Committee on March 19, 2009 voted overwhelmingly that a favorable benefit-risk profile had been demonstrated for use of rivaroxaban in the prophylaxis of venous thromboembolism (VTE) in patients undergoing hip or knee replacement surgery, but voiced some concerns about the strength of the signals for hepatotoxicity and the feasibility of long-term studies to further elucidate the hepatotoxicity potential. Subsequent to the advisory committee meeting, findings of the Division of Scientific Investigations (DSI) inspections of several sites, particularly in RECORD 4, identified deficiencies with regard to compliance with study procedures, completeness in reporting of adverse events and other irregularities during the conduct of the RECORD studies raising questions about the adequacy of study monitoring by Bayer and necessitating further examination of the integrity of the studies by DSI.

On May 27, 2010 the Agency issued a Complete Response (CR) letter to Johnson & Johnson (Appendix B) citing results from the DSI clinical investigator inspections indicating that some sites may be unreliable and results from the sponsor (Bayer) inspection revealing that "the sponsor failed to 1)ensure proper monitoring of the study, 2)to ensure that study was conducted in accordance with the protocol and/or investigational plan, and 3)to ensure that FDA and all investigators were promptly informed of significant new adverse effects or risks." The sponsor was requested to provide a detailed report of their clinical quality assurance (QA) audit plan including plan for securing investigator compliance, audit findings, corrective actions including termination of investigators, oversight of CROs and Bayer handling of review information obtained from the CROs. The sponsor was asked to plan and perform an additional audit and provide a full report.

Also, in the CR letter the sponsor was informed that the supplied clinical data were insufficient to fully characterize a potential risk for serious liver toxicity. The sponsor was asked to provide additional long-term safety data from the studies of rivaroxaban in patients with atrial fibrillation (ROCKET studies), post-marketing experience outside the U.S., final reports for other completed long-term treatment studies and summary of post-marketing studies initiated outside the U.S.

The CR letter also listed Chemistry, Manufacturing and Controls (CMC) deficiencies that needed to be addressed prior to product approval of the application.

In the resubmission the sponsor has provided a full response the CR letter. The submission includes:

- detailed information regarding the auditing and monitoring procedures and results for the RECORD studies (including the Bayer QA audit plans, SOPs, audit findings and corrective actions, and list of clinical investigators terminated for noncompliance for the RECORD studies; information on each CRO hired to monitor the clinical sites for the RECORD program, the oversight process for each CRO, and processes to ensure monitoring, as well as a list of noncompliant sites reported by the CROs; and the Bayer audits and the independent third party (b) (4) audits methodology, results and analyses, also including the results of the Sponsor's RECORD 4 study data verification). This information was reviewed by the

Division of Scientific Investigations (DSI) (See Compliance Review by Susan Thompson, M.D., 5/25/2011).

- Background information on the Hepatic Event Assessment Committee (HEAC) and a comprehensive Integrated Summary of Liver Safety
- Safety findings from post-marketing exposures outside the United States
- The protocol and safety findings from the observational post marketing study XAMOS
- The final study report for ATLAS ACS TIMI 46, including electronic datasets
- Reference to previous submissions indicating and including information about updated Bayer and J & J DMFs in support of the application. Information to address the deficiencies in drug substance information, drug product specifications, dissolution criteria, stability data and description of container and closure system information as requested in the CR letter. (See review by Chemistry, Manufacturing and Controls (CMC) (Joyce Z. Crich, Ph.D., 6/02/2011).
- A study synopsis and proposal to conduct a Phase 1 drug interaction study (RIVAROXACS1001) in patients with mild or moderate renal impairment concomitantly receiving erythromycin, a moderate CYP3A4/moderate P-gp inhibitor to address the Cinical Pharmacology recommendation that the sponsor develop a lower strength formulation for use in dose modification in certain populations of patients. The sponsor's arguments and information have been reviewed by Clinical Pharmacology (Joseph Grillo, Pharm.D. and Nitin Mehrotra, Ph.D., 6/03/2011).

Additional information was provided upon Division's request during the review cycle regarding occurrences of events of agranulocytosis, Stevens-Johnson syndrome, and neuraxial hematoma within the safety database of rivaroxaban (including all completed and ongoing clinical trials up to date and post-marketing experience).

Clinical review of the new data and updated safety information in the resubmission has been completed by Min Lu, M.D. (review signed 6/03/2011). Please see Dr. Lu's review for detailed presentation of the new and updated safety data and other information in the application. Important in the clinical review of the resubmission were the findings of the DSI review of audit and monitoring information for the four RECORD studies. See Dr. Thompson's Compliance Review (signed 5/25/2011) for detailed description and analysis of the audit results. All four RECORD studies were conducted by Bayer. Monitoring oversight for RECORD 1, 2 and 3 was done by Bayer while RECORD 4 was monitored by (b) (4) a contract research organization (CRO). After receipt of the CR letter, J & J contracted (b) (4) for an independent third party audit of the RECORD studies. This audit examined 30/617 sites encompassing 945/12729 (7.4%) of enrolled patients across the four studies. (For the individual studies percentage of sites examined ranged from 2.0% for RECORD 3 to 6.9% for RECORD 4 and percentage of patients from 2.8% for RECORD 3 to 9.9% for RECORD 4). DSI review of the audit information found deficiencies in all four studies. The DSI review comments that the audits of the RECORD 1, 2, and 3 studies found deficiencies in drug accountability but did not demonstrate systematic deficiencies in multiple aspects of the conduct of the trials that would bring into question data integrity from all study sites. However, for RECORD 4 the deficiencies in terms of both extent and scope were more pervasive than in the other three studies. Adequacy of monitoring was assessed as ineffective in identifying significant violations or in taking actions towards securing compliance. In the

RECORD 4 study 63.1% of audited patients were found to be inadequately monitored as compared to 25.5%-40.0% of audited patients in the other three studies. The (b) (4) audits revealed considerably more unreported adverse events in RECORD 4 (265 events) as compared to the other studies (37-110 events) as well as other deficiencies. There were 8 unreported serious adverse events noted in the (b) (4) audits, all in RECORD 4. Also, post-operative randomization (as opposed to protocol-specified pre-operative randomization) occurred in 39.0% of audited RECORD 4 patients as compared to 0.4%-0.5% of audited patients in RECORD 1, 2, and 3. (See DSI Compliance Review by Susan Thompson, M.D., final signature 5/25/2011, for details). Based on the overall findings the DSI review concluded that the data from RECORD 4 are not considered reliable in support of the indication. For RECORD 1, 2 and 3 studies the data were considered reliable for the application, excepting the following sites: Lenart, Porvaneckas, and Slappendel in RECORD 1; Corces, Yang Berumen and Ono in RECORD 2; and Brabants in RECORD 3. For RECORD 1, RECORD 2, and RECORD 3 the unreliable sites accounted for 220 (4.8%), 102 (2.3%) and 27 (1.1%) of total enrolled patients, respectively.

Efficacy: Clinical and Statistical review of the four RECORD studies during the first review cycle found demonstration of efficacy in each of the four studies. Overall, for the primary efficacy endpoint "Total VTE" the event rates (mITT population) for the rivaroxaban and enoxaparin groups, respectively were: 1.1% (18/1595) and 3.7% (58/1558) in RECORD 1; 2.0% (17/864) and 9.3% (81/869) in RECORD 2; 9.6% (79/824) and 18.9% (166/878) in RECORD 3; and 6.9% (67/965) and 10.1% (97/959) in RECORD 4. The efficacy result was driven by venographically diagnosed DVT; however, rivaroxaban appeared superior to the comparator arm in RECORD 1, 2, and 3 and with a trend favoring rivaroxaban in RECORD 4 for proximal VTE. (See Clinical Review by Min Lu, M.D. signed 4/2/2009 and Medical Team Leader Secondary Review/CDTL Review by Kathy Robie Suh, signed 5/27/2009 (attached to this review as Appendix A)).

Examination of the contribution of the above listed DSI assessed unreliable sites for RECORD 1, 2 and 3 finds the following contribution of these sites to the primary efficacy evaluation:

Primary Efficacy Endpoint Event ("Total VTE") in RECORD 1, 2 and 3 Studies DSI Unreliable Sites (mITT Population)

	Rivaroxaban		Enoxaparin	
	Total patients	VTE	Total patients	VTE
RECORD 1:				
Lenart (Hungary)	41	0	40	1
Porvaneckas (Lithuania)	28	0	30	0
Slappendel (The Netherlands)	13	1	15	0
RECORD 2:				
Corces (USA)	9	0	9	1
Yang (China)	11	0	12	5
Naraffete (Mexico)	6	0	8	4
Ono (Brazil)	10	0	10	1
RECORD 3:				
Brabants (Belgium)	11	0	7	2

For RECORD 1 a single VTE event is excluded from each of the treatment arms. For RECORD 3 two events in the enoxaparin arm are excluded. These exclusions would not appear to have a meaningful effect on the overall efficacy result for these two studies. For RECORD 2 a total of 11 events in the enoxaparin arm and no events in the rivaroxaban arm are excluded. While these exclusions may not significantly affect the overall efficacy result for the study, the imbalance in the VTE exclusions between the treatment arms narrows the efficacy difference between the two arms. In interpreting these numbers it should be borne in mind that only a small fraction of the total sites and total patients enrolled were audited; therefore, interpreting the results involves some assumptions, such as that the audited sites were reasonably representative of all the sites where the studies were conducted with regard to types and extent of deficiencies. For RECORD 2 the occurrence of the primary efficacy endpoint by geographic area is shown in the table below (includes DSI unreliable sites). Though the finding is numerically skewed in the unreliable sites, qualitatively it is consistent with the overall RECORD 2 study efficacy results.

Incidence of Primary Efficacy Endpoint ("Total VTE") by Geographic Region (mITT Population)

	VTE/total patients	
	Rivaroxaban	Enoxaparin
Total	17/864	81/869
Australia	0/7	0/7
Brazil	2/61	6/55
Canada	0/47	1/44
China	1/121	16/122
Colombia	6/50	9/56
Denmark	0/64	2/58
Estonia	0/24	1/33
India	0/9	0/10
Indonesia	¼	0/4
Korea (South)	0/41	0/44
Latvia	0/15	0/19
Lithuania	1/64	3/60
Mexico	0/10	5/13
New Zealand	0/3	0/0
Norway	1/46	4/42
Peru	3/58	8/65
Portugal	0/4	0/5
South Africa	0/44	8/43
Sweden	0/103	6/101
United Kingdom	2/64	9/64
United States	0/25	3/24

With regard to efficacy, overall, the results support that rivaroxaban is effective in reducing VTE events in patients undergoing hip or knee surgery. However, considering the shortcoming in the monitoring adequacy in the studies, quantitative expression of that effectiveness as compared to the enoxaparin comparator in these studies may not be reliable. I would not conclude superiority of rivaroxaban over enoxaparin for the indication based on the results of these studies.

Safety: With regard to safety, among the audited sites (b) (4) in all four RECORD studies there were unreported adverse events (AE). The number of these events was greatest for RECORD 4 (265 unreported AE in 151 patients). For RECORD 1 there were 113 unreported AE in 66 patients; for RECORD 2, there were 131 unreported AE in 69 patients; and for RECORD 3 there were 37 unreported AE in 31 patients. For RECORD 4, revisiting of sites by (b) (4) for data verification audits of sites that had been audited (b) (4) revealed many additional unreported AEs, including serious adverse events. The (b) (4) audits identified 8 unreported SAEs, all from RECORD 4; the RECORD 4 (b) (4) audits revealed an additional 28 newly reported SAEs in 25 subjects (15 rivaroxaban, 12 enoxaparin, and 1 never randomized). The events included 2 newly-reported cases of ALT>3x ULN concurrent with a total bilirubin >2 x ULN (both in the enoxaparin arm); no new cases of DVT, PE or death were identified. The Compliance Review did not indicate any instances where reported adverse events were discovered to be attributed to the wrong patient or found not to have occurred.

Results of my examination of the important safety events in the clinical sites in the RECORD studies 1, 2, and 3 that were assessed unreliable are summarized in the following table:

Occurrence of Serious Adverse Events in RECORD 1, 2 and 3 Studies DSI Unreliable Sites (randomized subjects)

	Rivaroxaban			Enoxaparin		
	Total patients	SAE	Deaths	Total patients	SAE	Deaths
RECORD 1:						
Lenart (Hungary)	44	2	0	44	3	0
Porvaneckas (Lithuania)	36	4	0	36	1	0
Slappendel (The Netherlands)	31	5	0	30	2	0
RECORD 2:						
Corces (USA)	9	0	0	10	2	0
Yang (China)	17	0	0	17	0	0
Naraffete (Mexico)	13	0	0	12	6	2
Ono (Brazil)	12	0	0	12	1	0
RECORD 3:						
Brabants (Belgium)	14	1	0	13	1	0

In RECORD 1, overall the incidence of SAEs was 6.6% (146/2209) in the rivaroxaban arm and 8.1% (181/2224) in the enoxaparin arm. In RECORD 2, the incidence was 7.3% (90/1228) for rivaroxaban and 10.7% (131/1229) for enoxaparin, and in RECORD 3, it was 7.4% (90/1220) for rivaroxaban and 8.9% (110/1239) for enoxaparin. Types of SAEs at the unreliable sites were similar to those reported overall in the studies. The incidence of major bleedings in RECORD 1 was 0.27% (6/2209) in the rivaroxaban arm and 0.13% (3/2224) in the enoxaparin arm. In RECORD 2, the incidence was 0.8% (1/1228) for rivaroxaban and 0.8% (1/1229) for enoxaparin, and in RECORD 3, it was 0.66% (8/1220) for rivaroxaban and 0.65% (8/1239) for enoxaparin. No patients at any of the unreliable sites in these studies were reported as having a major bleeding event. Though there may be concerns about the quantitative accuracy of the reported safety events in for these sites, in general, it appears that the safety findings for these unreliable sites were consistent with the overall safety findings for the studies.

Statistical Review of the safety evaluation for possible liver toxicity during the first cycle was done by Chava Zibman, Ph.D. (2/26/2009). That review was based on aggregate data from the four RECORD studies, which all involved treatment with rivaroxaban or enoxaparin for 35 days or less. The review commented that, "Because of the structure of the data and issues associated with data quality, no formal statistical inference was conducted" in the analysis. Rather, the review summarized the liver assessment test results and frequencies of hepatobiliary adverse events. The review concluded that based on the data reviewed, "it might be difficult to differentiate between Rivaroxaban and Enoxaparin" patients based on signals of liver toxicity in the data". Review and comment on potential for liver toxicity during the first review cycle was also provided from the Office of Surveillance and Epidemiology (OSE), Division of Epidemiology (DEPI) (Kate Gelperin, M.D., M.P.H., 2/13/2009). Dr. Gelperin's review highlighted previous FDA experience with assessment of severe drug-induced liver injury due to ximelagatran, an anticoagulant drug (direct thrombin inhibitor) developed for similar indications, where no cases of severe liver injury were found in the short-term (orthopedic) clinical trials; however, a strong signal was subsequently identified in long-term (atrial fibrillation) trials and also summarized the regulatory history including withdrawals and risk management for drug-induced liver injury. For rivaroxaban, the DEPI review concluded that a potential signal for severe liver injury associated with rivaroxaban therapy has not been fully characterized by the RECORD studies and recommended that full evaluation of safety data from long-term clinical trials be done to inform decisions about the balance of therapeutic benefit versus risk with rivaroxaban.

During the current review cycle, Statistical Review and Evaluation of potential risk for serious liver toxicity was done by John S. Yap, Ph.D. (6/10/2011). The review assessed liver toxicity based on the results of five trials of rivaroxaban at dose of 10-30 mg daily for chronic use (>35 days and up to 4 years) for stroke prevention in patients with atrial fibrillation (ROCKET and J-ROCKET studies), and for treatment in patients with deep venous thrombosis (EINSTEIN-DVT study or pulmonary embolism (EINSTEIN-PE) and extended DVT/PE treatment (EINSTEIN Extension study). The proportions of patients with elevated alanine aminotransferase (ALT) at predefined multiples of the upper limit of normal (ULN) were generally balanced between the rivaroxaban and warfarin arms in the atrial fibrillation trials and were lower in some cases in the rivaroxaban arm as compared to the enoxaparin arm in the VTE studies. Occurrence of "Hy's Law" cases (concurrent values of ALT>3x ULN and total bilirubin >2x ULN) in the atrial fibrillation studies was similar in the rivaroxaban (0.45%; 34/7618) and warfarin (0.47%; 36/7650) arms. In the DVT/PE treatment studies overall Hy's Law cases were 0.17% (6/3560) with rivaroxaban ttreatment and 0.17% (6/3487) with enoxaparin. In the DVT extended treatment study there were no Hy's Law cases. The review concluded that in the controlled long-term studies the liver toxicity profile is comparable in the rivaroxaban and control groups.

Rivaroxaban was approved in Canada and European Union for prophylaxis of VTE in patients undergoing hip or knee replacement surgery in September 2008 and is approved in some other countries as well. Post-marketing safety information and safety information from an observational post-marketing safety study were included in the resubmission. The most common serious adverse events reported were bleeding events. Other serious adverse events in the reports were cerebral hemorrhage (9 cases, 3 deaths), agranulocytosis (3 cases; 1 death), hypersensitivity

reactions (3 cases; no deaths) anaphylactic shock (2 cases; no deaths); anaphylactic reaction (2 cases; no deaths); Stevens-Johnson syndrome (2 cases; no deaths).

There was no advisory committee meeting for rivaroxaban during this review cycle.

Conclusions and Recommendations:
The resubmission confirms serious monitoring and reporting problems within the RECORD studies, particularly for RECORD 4 to the extent that data from RECORD 4 cannot be considered reliable. For the remaining RECORD studies, though each had serious problems necessitating exclusion of data from one or more audited sites, overall the result for the studies appear sufficiently robust to support that rivaroxaban is efficacious for the proposed use. The additional safety data from long-term studies do not identify a risk of serious hepatotoxicity as compared to the active comparators (enoxaparin and warfarin) with rivaroxaban as used and managed in these studies. The major safety risk for rivaroxaban is bleeding. In addition, cases of agranulocytosis and Stevens-Johnson syndrome have been reported. The overall safety profile of rivaroxaban appears acceptable for approval; however serious events should be clearly described in the labeling and be considered for focused post-marketing monitoring.

Overall, the benefit/risk for rivaroxaban appears acceptable for approval for the proposed indication. The wording of the indication statement should be the same as for other products approved for the indication --- "for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery and in patients undergoing knee replacement surgery". The treatment duration should be 35 days for patients undergoing hip replacement surgery and 12 days for patients undergoing knee replacement surgery, to reflect actual treatment durations in the studies.

Rivaroxaban does not appear to provide a unique benefit, other than convenience of oral administration, over the other products already approved for the proposed indications. Qualitatively, the benefits and risks appear similar. Accordingly, the labeling for rivaroxaban should be consistent with the labeling for the other products with regard to display of the efficacy results and inclusion of relevant warnings for anticoagulation in these patients. Quantitatively, because of the issues with the quality of the data collection for the studies, conclusions regarding relative efficacy of rivaroxaban and enoxaparin for these uses should not be drawn from the studies. Exact wording of labeling will be developed with input and discussion of the entire review team.

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/s/

KATHY M ROBIE SUH
06/13/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-406/059
Priority or Standard	Resubmission
Submit Date(s)	23-Dec-2010
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Division / Office	DHP/OODP
Reviewer Name(s)	Min Lu, M.D., M.P.H.
Review Completion Date	1-June-2011
Established Name	Rivaroxaban
(Proposed) Trade Name	XARELTO®
Therapeutic Class	Anticoagulant
Applicant	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Formulation(s)	Oral tablet
Dosing Regimen	10 mg once daily
Indication(s)	Prophylaxis of Deep Vein Thrombosis (DVT)
Intended Population(s)	Patients undergoing hip or knee replacement surgery

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, rivaroxban is acceptable to be approved for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing hip or knee replacement surgeries.

1.2 Risk Benefit Assessment

Rivaroxaban has been shown to reduce the rate of total venous thromboembolic events (VTE) in patients undergoing hip or knee replacement surgery as compared to the control (enoxaparin or enoxaparin followed by placebo). Four randomized controlled trials (RECORD 1-4) were conducted to support the currently proposed indication in patients undergoing hip or knee replacement surgeries. Rivaroxaban reduced the rate of total venous thromboembolic event (VTE) as compared to the control (enoxaparin or enoxaparin followed by placebo) in patients undergoing hip surgery (RECORD 1: 1.1% vs. 3.7%, respectively, $p<0.001$; RECORD 2: 2.0% vs. 9.3% [enoxaparin/placebo], respectively; $p<0.001$) and in patients undergoing knee replacement surgery (RECORD 3: 9.6% vs. 18.9%, respectively, $p<0.001$; RECORD 4: 6.9% vs. 10.1%, respectively; $p<0.05$). The rate of total VTE remained statistically significantly lower in the rivaroxaban group as compared to the control in patients undergoing hip surgery (RECORD 1: 1.1% vs. 3.9% [enoxaparin], respectively, $p<0.001$; RECORD 2: 2.1% vs. 8.4% [enoxaparin/placebo], respectively; $p<0.001$) and in patients undergoing knee replacement surgery (RECORD 3: 9.6% vs. 18.9%, respectively, $p<0.001$; RECORD 4: 7.5% vs. 10.7%, respectively, $p<0.05$) after unreliable clinical sites were excluded from the analysis. The difference between the two treatment groups was mainly due to asymptomatic DVT detected by venogram in all studies.

The major risk of rivaroxban treatment is bleeding complication. In RECORD studies, the incidence of major bleeding was higher with rivaroxaban treatment (24, 0.39%) than with enoxaparin (13, 0.21%). One fatal bleeding event (gastrointestinal bleeding) was reported after rivaroxaban treatment as compared to none with enoxaparin. Two patients experienced critical organ bleeding events after rivaroxaban treatment (retinal hemorrhage and adrenal hemorrhage) as compared to 5 patients in the enoxaparin group (catheter-site hemorrhage, subdural hemorrhage, extradural hematoma, catheter-related complication, and spinal epidural hemorrhage). Bleeding events requiring re-operation occurred in 12 (0.19%) subjects in rivaroxaban group as compared to 7 (0.11%) subjects in the enoxaparin group. More patients experienced clinically overt extrasurgical site bleeding associated with a >2 g/dL decrease in hemoglobin or requiring blood transfusion >2 units in the rivaroxaban group (8, 0.13%) than in the enoxaparin group (1, 0.02%). The incidence of major bleeding was relatively higher in the total knee replacement (TKR) patients (0.62% with rivaroxaban and 0.36% with enoxaparin) compared to the total hip replacement (THR) patients (0.20% with rivaroxaban and 0.09% with enoxaparin). In the RECORD studies, the incidence of clinically relevant non-major bleeding

was also higher in the rivaroxaban group (177, 2.86%) than the enoxaparin group (145, 2.34%). The bleeding events reported more frequently in the rivaroxaban group than in the enoxaparin group were macroscopic hematuria (0.45% vs. 0.13%), rectal bleeding (0.32% vs. 0.1%), nose bleeding (>5 minutes) (0.13% vs. 0.06%), and vaginal bleeding (0.13% vs. 0.03%). Overall, the incidence of any bleeding was 7.0% in the rivaroxaban group as compared to 6.5% in the enoxaparin group. In subgroup analyses, Asian subjects, subjects with body weight ≤50 kg or >110 kg, subjects with BMI<18.5 or ≥40, or patients with severe renal impairment (creatinine clearance <30 mL/min) showed a higher risk of major or non-major clinically relevant bleeding events with rivaroxaban as compared to other groups.

The other adverse events reported more frequently with rivaroxaban as compared to the control were pruritus, wound healing complications, pain in extremity, increased muscle tone and cramping, wound secreation, blister, syncope, and dysuria in clinical trials. Other significant adverse events reported associated with rivaroxaban treatment in post-marketing spontaneous reports were cerebral hemorrhage, epidural hematoma, hypersensitivity reactions including anaphylactic shock, agranulocytosis, and Steven-Johnson syndrome.

The potential for liver toxicity with rivaroxaban was evaluated in long-term clinical studies for prevention of stroke in patients with atrial fibrillation (warfarin as comparator), for indication of treatment of VTE in patients with symptomatic VTE (enoxaparin/VKA as comparator), and in patients with acute coronary syndrome (placebo as comparator in a phase 2 study). Overall, ALT >3 xULN was reported at a similar rate (2.5%) in the rivaroxaban group as compared to the comparator (2.3%) in the pooled analysis. The incidence of ALT abnormalities at different threshold (>5 xULN, 8 xULN, >10 xUN or >20 xULN) was similar between the rivaroxaban and the comparators. The overall incidence of ALT >3 x ULN with total bilirubin >2 x ULN in the rivaroxaban group (0.30%) was also comparable to that of the comparator (0.36%) in those long-term clinical studies. The overall incidence of reported hepatic adverse events and serious hepatic adverse events were similar between the rivaroxaban and the comparators in those trials. The overall number of cases with ALT >3 x ULN and total bilirubin >2 x ULN assessed to be possibly or probably related to the study drug was comparable in both treatment groups by an independent hepatic event assessment committee (HEAC) (0.03% vs. 0.01% by all 3 reviewers, 0.06% vs. 0.05% by at least 2 reviewers, and 0.11% vs. 0.13% by at least 1 review). No cases were considered to be definitely related to the study drug. In most rivaroxaban cases that were considered to be possibly related to rivaroxaban treatment, the events were resolved between 1 week and 2 months after rivaroxaban discontinued and in few cases the events resolved while rivaroxaban was continued. In postmarketing reports, cases of jaundice and symptomatic hepatitis were reported after rivaroxaban treatment and were considered to be possibly or probably related to the treatment. In most cases the events were resolved after rivaroxaban was discontinued.

The overall benefit of rivaroxaban treatment is considered to outweigh the risk for the proposed use in the intended population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Xarelto (rivaroxaban) is a selective Factor Xa (FXa) inhibitor with oral bioavailability and is under development as an oral anticoagulant for multiple indications. The currently proposed use is for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgeries. The proposed dose of rivaroxaban is 10 mg once daily administered orally. The proposed treatment duration for rivaroxaban is 35 days for patients undergoing hip replacement surgery and 14 days for patients undergoing knee replacement surgery.

This is the second review cycle for this NDA. The original NDA, which included the four RECORD studies, was submitted on July 22, 2008 and an Advisory Committee Meeting was held on March 19, 2009. See my previous review (Min Lu, M.D., M.P.H., 4/2/2009) for detailed evaluations for these studies. The Agency issued a Complete Response (CR) on May 27, 2009. The Letter listed several deficiencies that included data quality issues identified by the Division of Scientific Investigation, insufficient long-term clinical data to fully characterize a potential risk for serious liver toxicity, and inadequate drug master file (DMF) information to support the NDA.

To address the liver toxicity issue, the Agency requested the following information from the sponsor:

a. A report that assesses the potential signal for severe liver toxicity in your major on-going clinical studies of patients with atrial fibrillation (the "ROCKET" studies). Provide this report in a manner that does not compromise the analytical integrity of these studies. Base this report upon the findings from a data safety monitoring board's review of the clinical information for patients reported to have serum alanine aminotransferase (ALT) values greater than three times the upper limit of normal along with serum total bilirubin values greater than twice the upper limit of normal. The board's review should, at a minimum, consist of the review of all available clinical data for the index patients along with the treatment assignment. In reviewing these data, the board should consider any possible imbalance in the occurrence of the liver test abnormalities as well as each patient's clinical features, particularly those related to liver abnormalities. We welcome a discussion with you to address the most appropriate method to report the board's findings to us.

b. A report of the safety findings from the rivaroxaban post-marketing experience outside the United States. Include tabular and text summaries of spontaneously reported adverse events and an estimate of the numbers of patients exposed in the market place.
c. A report that provides a summary of post-marketing studies initiated outside the United States, to include a description of the study designs, a status update (e.g., date of initiation, numbers of enrolled subjects) as well as a summary of adverse events detected in these studies. Additionally, provide a copy of the protocol for the "observational" postmarketing study you cited at the March 19, 2009, Advisory Committee.
d. Provide a final report for the "ATLAS ACS TIMI 46" study, including electronic datasets sufficient to verify the safety and efficacy data.

In this submission, the applicant submitted a complete response and included long-term liver safety data from recently completed phase 3 studies for prevention of stroke in patients with atrial fibrillation (ROCKET studies), for treatment of venous thromboembolic events (EINSTEIN studies), ATLAS ACS TIMI 46 study, and post-marketing data from other countries where the drug is approved.

This review will focus on the submitted liver safety data from recently completed long-term clinical trials and post-marketing data in patients undergoing hip or knee replacement surgeries in other countries. Other important adverse reaction from the submitted data will also be reviewed.

At the same time, the applicant has also submitted a separate NDA (NDA 20-2439) for rivaroxaban to the Division of Cardiovascular and Renal Products for the indication for the prevention of stroke in patients with atrial fibrillation. That application is currently under review.

3 Ethics and Good Clinical Practices

See Division of Scientific Investigations (DSI) review for the additional audit findings for RECORD 1-4 studies (by Dr. Susan Thompson, M.D. dated 5/25/2011). No additional clinical studies are conducted for the proposed indication since the Agency's CR. Recently completed and ongoing long-term studies evaluated for liver toxicity have not been inspected by DSI.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See CMC review.

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

N/A

4.4 Clinical Pharmacology

See Clinical Pharmacology review.

5 Sources of Clinical Data

No additional clinical studies were conducted for the proposed indication since the Agency's CR. See previous clinical review for the clinical data for the proposed indication.

This submission has provided long-term liver safety data from recently completed clinical trials and ongoing trials for other indications and post-marketing experience in other countries in patients undergoing hip or knee replacement surgeries. See Section 6 for detailed clinical data submitted for liver safety evaluation and safety update for the proposed indication.

6 Review of Efficacy

Efficacy Summary

The efficacy for the proposed indication has been reviewed previously (see my review dated 4/2/2009). The efficacy results are briefly summarized below. No new efficacy data are submitted in this resubmission.

Four randomized controlled trials (RECORD 1-4) were conducted to support the currently proposed use in patients undergoing hip or knee replacement surgeries. Rivaroxaban was shown to reduce the rate of total venous thromboembolic event (VTE) as compared to the control (enoxaparin or enoxaparin followed by placebo) in patients undergoing hip surgery (RECORD 1: 1.1% vs. 3.7%, respectively, $p<0.001$; RECORD 2: 2.0% vs. 9.3% [enoxaparin/placebo], respectively; $p<0.001$) and in patients undergoing knee replacement surgery (RECORD 3: 9.6% vs. 18.9%, respectively, $p<0.001$; RECORD 4: 6.9% vs. 10.1%, respectively; $p<0.05$). The results of the secondary efficacy endpoints were consistent with the primary efficacy endpoint. The major VTE rate (consisted of VTE-related death, non-fatal PE, or proximal DVT) was also significantly lower in rivaroxaban group as compared to the enoxaparin group in patients undergoing hip surgery (RECORD 1: 0.2% vs. 2.0%, respectively, $p<0.001$; RECORD 2: 0.6% and 5.1% [enoxaparin/placebo], respectively; $p<0.001$) and in one of two studies in patients undergoing knee replacement surgery (RECORD 3: 1.0% and 2.6%, respectively; $p<0.05$; RECORD 4: 1.2% and 2.0%, respectively, $p>0.05$). The symptomatic VTE rate was significantly lower with rivaroxaban than with enoxaparin in one of two studies in patients undergoing hip surgery (RECORD 1: 0.27% vs. 0.49%, respectively, $p>0.05$; RECORD 2: 0.24% vs. 1.22%[enoxaparin/placebo], respectively, $p<0.05$) and in one of two studies in patients

undergoing knee replacement surgery (RECORD 3: 0.66% vs. 1.94%, respectively, p<0.05; RECORD 4 0.72% vs. 1.19% respectively, p>0.05).

The primary efficacy results in patients undergoing total hip replacement (THR) surgery and in patients undergoing total knee replacement (TKR) are summarized in the tables below:

Efficacy Results in THR Trials: Primary Efficacy Endpoint in MITT population

	RECORD 1		**RECORD 2**	
Endpoint	Rivaroxaban 10mg qd N=1595	Enoxaparin 40mg qd N=1558	Rivaroxaban 10mg qd N=864	Enoxaparin 40 mg qd + Placebo N=869
Total VTE	18 (1.1%)[a]	58 (3.7%)	17 (2.0%)[a]	81 (9.3%)
All cause death	4 (0.3%)	4 (0.3%)	2 (0.2%)	6 (0.7%)
Nonfatal PE	4 (0.3%)	1 (<0.1%)	1 (0.1%)	4 (0.5%)
Proximal DVT	1 (<0.1%)	31 (2.0%)	5 (0.6%)	44 (5.1%)
Distal DVT	12 (0.8%)	27 (1.7%)	11 (1.3%)	49 (5.6%)

a: p<0.001

Efficacy Results in TKR Trials: Primary Efficacy Endpoint in MITT population

	RECORD 3		**RECORD 4**	
Endpoint	Rivaroxaban 10mg qd N=824	Enoxaparin 40mg qd N=878	Rivaroxaban 10mg qd N=965	Enoxaparin 30mg bid N=959
Total VTE	79 (9.6%)[a]	166 (18.9%)	67 (6.9%)[b]	97 (10.1%)
All cause death	0	2 (0.2%)	2 (0.2%)	3 (0.3%)
Nonfatal PE	0	4 (0.5%)	5 (0.5%)	8 (0.8 %)
Proximal DVT	9 (1.1 %)	20 (2.3%)	8 (0.8%)	14 (1.5%)
Distal DVT	74 (9.0 %)	156 (17.8%)	57 (5.9%)	82 (8.6%)

a: p<0.001; b: p=0.012

The Division of Scientific Investigation (DSI), Office of Compliance has reviewed the resubmission and identified the following study sites as unreliable in the RECORD studies based on additional audit findings (see review by Dr. Susan Thompson, M.D. dated 5/25/2011).

- RECORD 1: 3 sites
  - Site 46002: 87 subjects
  - Site 57001: 72 subjects
  - Site 30002: 61 subjects
- RECORD 2: 4 sites
  - Site 14010: 19 subjects
  - Site 54005: 34 subjects
  - Site 32005: 25 subjects
  - Site 50005: 24 subjects
- RECORD 3: 1 site
  - Site 28015: 27 subjects
- RECORD 4: 8 sites
  - Site 14029: 92 subjects
  - Site 32006: 42 subjects
  - Site 14005: 152 subjects
  - Site 14010: 203 subjects
  - Site 14004: 61 subjects
  - Site 60010: 68 subjects
  - Site 32002: 46 subjects
  - Site 60006: 80 subjects

The DSI reviewer concluded that the data generated by the RECORD 4 study was unreliable based on and recommends that the data not be used in support the proposed indication. The data from RECORD 1-3 were considered to be reliable, except the identified sites mentioned above.

The FDA statistical reviewer (Dr Qing Xu, Ph.D) performed additional efficacy analysis for each RECORD study including RECORD 4 after excluding the above unreliable sites. The rate of total VTE remained statistically significantly lower in the rivaroxaban group as compared to the control group in all RECORD studies. The results are shown in Table below.

Total VTE in MITT Population after Excluding Unreliable Sites in Each Study

Studies	Rivaroxaban	Enoxaparin	P-value
RECORD 1	17/1513 (1.1%)	57/1473 (3.9%)	P<0.0001
RECORD 2	17/847 (2.0%)	70/835 (8.4%)	P<0.0001
RECORD 3	79/813 (9.7%)	164/871 (18.8%)	P<0.0001
RECORD 4	53/711 (7.5%)	75/702 (10.7%)	P<0.05

Overall, rivaroxaban demonstrated efficacy in the prophylaxis of total VTE in patients undergoing total elective hip or knee replacement surgery in the studies. The difference between

the two treatments was mainly due to asymptomatic DVT detected by venogram. The efficacy data are adequate to support the indication for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing hip or knee replacement surgeries.

7 Review of Safety

Safety Summary

The safety of rivaroxaban for the proposed indication in patients undergoing hip or knee replacement surgeries in clinical trials has been reviewed previously (see my review dated 4/2/2009). The main safety results are briefly summarized below.

The major risk of rivaroxban treatment is bleeding. In the RECORD studies, the incidence of major bleeding was higher with rivaroxaban treatment (24, 0.39%) than with enoxaparin (13, 0.21%). One fatal bleeding event (gastrointestinal bleeding) was reported after rivaroxaban treatment as compared to none with enoxaparin. Two patients experienced critical organ bleeding events after rivaroxaban treatment (retinal hemorrhage and adrenal hemorrhage) as compared to 5 patients in the enoxaparin group (catheter-site hemorrhage, subdural hemorrhage, extradural hematoma, catheter-related complication, and spinal epidural hemorrhage). Bleeding events requiring re-operation occurred in 12 (0.19%) subjects in the rivaroxaban group as compared to 7 (0.11%) subjects in the enoxaparin group. More patients experienced clinically overt extrasurgical site bleeding associated with a >2 g/dL decrease in hemoglobin or requiring blood transfusion >2 units in the rivaroxaban group (8, 0.13%) than in the enoxaparin group (1, 0.02%). The incidence of major bleeding was relatively higher in the TKR patients (0.62% with rivaroxaban and 0.36% with enoxaparin) compared to the THR patients (0.20% with rivaroxaban and 0.09% with enoxaparin). In the RECORD studies, the incidence of clinically relevant non-major bleeding was also higher in the rivaroxaban group (177, 2.86%) than the enoxaparin group (145, 2.34%). The bleeding events reported more frequently in the rivaroxaban group than in the enoxaparin group were macroscopic hematuria (0.45% vs. 0.13%), rectal bleeding (0.32% vs. 0.1%), nose bleeding (>5 minutes) (0.13% vs. 0.06%), and vaginal bleeding (0.13% vs. 0.03%). Overall, the incidence of any bleeding was 7.0% in the rivaroxaban group as compared to 6.5% in the enoxaparin group. In subgroup analyses, Asian subjects, subjects with body weight ≤50 kg or >110 kg, subjects with BMI<18.5 or ≥40, or patients with severe renal impairment (creatinine clearance <30 mL/min) the risk of major or non-major clinically relevant bleeding events appear to be higher with rivaroxaban as compared to other groups.

The other adverse events were reported more frequently (0.5% increase if total events >100 or 0.3 increase if total events 50-100) with rivaroxaban as compared to the control were pruritus, wound healing complications, pain in extremity, increased muscle tone and cramping, wound secretion, blister, syncope, and dysuria in clinical trials.

The following tables summarize the bleeding events and overall adverse events in pooled RECORD 1-4 studies.

Bleeding Events in RECORD 1-4

	THR: RECORD 1-2		TKR: RECORD 3-4		Overall	
Bleeding Events	Rivaroxaban N=3437	Enoxaparin N=3453	Rivaroxaban N=2746	Enoxaparin N=2747	Rivaroxaban N=6183	Enoxaparin N=6200
Major Bleeding	7 (0.20%)	3 (0.09%)	17 (0.62%)	10 (0.36%)	24 (0.39%)*	13 (0.21%)
-Fatal bleeding	1 (0.03%)	0	1 (0.04%)	0	2 (0.03%)	0
-Bleeding into a critical organ	1 (0.03%)	1 (0.03%)	2 (0.07%)	4 (0.15 %)	3 (0.05%)	5 (0.08 %)
-Bleeding that required re-operation	2 (0.06%)	1 (0.03%)	10 (0.36%)	6 (0.22%)	12 (0.19%)	7 (0.11%)
-Clinically overt extrasurgical site bleeding associated with a >2 g/dL decrease in Hb	3 (0.09%)	1 (0.03%)	5 (0.18%)	0	8 (0.13%)	1 (0.02%)
-Clinically overt extrasurgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.09%)	1 (0.03%)	5 (0.18%)	0	8 (0.13%)	1 (0.02%)
Any bleeding event	214 (6.2%)	199 (5.8%)	220 (8.0%)	202 (7.4%)	434 (7.0%)	401 (6.5%)

*p=0.076

Summary of Adverse Events
(Subjects Valid for Safety Analysis in Pooled RECORD 1-4 Studies)

Preferred Term	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
Any AEs	**4179 (67.6%)**	**4306 (69.5%)**
Any SAEs	**406 (6.6%)**	**528 (8.5%)**
Any death	**13 (0.2%)**	**25 (0.4%)**
Any adverse event resulting in permanent	**230 (3.7%)**	**288 (4.7%)**

discontinuation of study drug		
AEs occurred ≥ 1%		
Nausea	788 (12.7%)	797 (12.9%)
Pyrexia	719 (11.6%)	712 (11.5%)
Vomiting	605 (9.8%)	610 (9.8%)
Constipation	573 (9.3%)	596 (9.6%)
Peripheral edema	419 (6.8%)	409 (6.6%)
Anemia postoperative	352 (5.7%)	355 (5.7%)
Procedural pain	322 (5.2%)	345 (5.6%)
Hypotension	313 (5.1%)	315 (5.1%)
Insomnia	307 (5.0%)	326 (5.3%)
Dizziness	259 (4.2%)	243 (3.9%)
Anemia	244 (4.0%)	244 (3.9%)
Pruritus	225 (3.6%)	202 (3.3%)
Pain in extremity	203 (3.3%)	167 (2.7%)
Diarrhea	158 (2.6%)	182 (2.9%)
Hemoglobin decreased	157 (2.5%)	166 (2.7%)
Urinary retention	156 (2.5%)	149 (2.4%)
Headache	153 (2.5%)	151 (2.4%)
Muscle spasms	148 (2.4%)	115 (1.9%)
Tachycardia	146 (2.4%)	149 (2.4%)
Wound secretion	146 (2.4%)	106 (1.7%)
ALT increased	134 (2.2%)	183 (3.0%)
GGT increased	119 (1.9%)	173 (2.8%)
Urinary tract infection	118 (1.9%)	125 (2.0%)
AST increased	110 (1.8%)	140 (2.3%)
Erythema	112 (1.8%)	102 (1.7%)
Arthralgia	103 (1.7%)	141 (2.3%)
Blister	104 (1.7%)	68 (1.1%)
Asthenia	102 (1.7%)	104 (1.7%)
Fatigue	107 (1.7%)	109 (1.8%)
Body temperature increased	92 (1.5%)	119 (1.9%)
Hypertension	88 (1.4%)	86 (1.4%)
somnolence	85 (1.4%)	81 (1.3%)
Anxiety	83 (1.3%)	70 (1.1%)
Rash	83 (1.3%)	87 (1.4%)
Hypokalemia	79 (1.3%)	108 (1.7%)
Dyspepsia	78 (1.3%)	91 (1.5%)
LDH increased	77 (1.3%)	83 (1.3%)
Dyspnea	77 (1.3%)	83 (1.3%)
Thrombocythemia	73 (1.2%)	70 (1.1%)
Hematoma	61 (1.0%)	72 (1.2%)
Abdominal pain upper	62 (1.0%)	51 (0.8%)
Syncope	60 (1.0%)	38 (0.6%)

Additional safety analysis was performed after RECORD 4 was excluded from the pooled analysis due to the DSI recommendations. The overall bleeding events excluding RECORD 4 are presented below.

Major Bleeding Events in RECORD 1-3

	THR: RECORD 1-2		**TKR: RECORD 3**		**Overall**	
Bleeding Events	Rivaroxaban N=3437	Enoxaparin N=3453	Rivaroxaban N=1220	Enoxaparin N=1239	Rivaroxaban N=6183	Enoxaparin N=6200
Major Bleeding	7 (0.20%)	3 (0.09%)	7 (0.57%)	6 (0.48%)	14 (0.30%)	9 (0.19%)
-Fatal bleeding	1 (0.03%)	0	0	0	1 (0.02%)	0
-Bleeding into a critical organ	1 (0.03%)	1 (0.03%)	1 (0.08%)	2 (0.16 %)	2 (0.04%)	3 (0.06 %)
-Bleeding that required re-operation	2 (0.06%)	1 (0.03%)	5 (0.41%)	4 (0.32%)	7 (0.15%)	5 (0.11%)
-Clinically overt extrasurgical site bleeding associated with a >2 g/dL decrease in Hb	3 (0.09%)	1 (0.03%)	1 (0.08%)	0	4 (0.09%)	1 (0.02%)
-Clinically overt extrasurgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.09%)	1 (0.03%)	1 (0.08%)	0	4 (0.09%)	1 (0.02%)
Any bleeding event	214 (6.2%)	199 (5.8%)	60 (4.9%)	60 (4.8%)	274 (5.9%)	259 (5.5%)

In the RECORD 4 study, major bleeding occurred in 10 patients in the rivaroxaban group (0.7%) and 4 patients in the enoxaparin group (0.3%). Rivaroxaban group in RECORD 4 had the highest bleeding rate among the RECORD studies. The following describes the major bleeding cases in RECORD 4 including reported clinical sites:

Rivaroxaban cases:

- 1 fatal GI bleeding (the only fatal case in all RECORD studies)- at unreliable clinical site 14010 (US)
- 1 critical organ bleeding: adrenal hemorrhage- at unreliable clinical site 14004 (US)
- 4 clinically overt extra-surgical site bleeding associated with a fall in hemoglobin of 2 g/dL or more and leading to transfusion of 2 or more units of whole blood or packed cells -at clinical sites: 14011 (US), 90001 (Sri Lanka), 26013 (Canada), 14004 (adrenal bleeding, US)
- 5 bleeding leading to re-operation-at clinical sites: 35006 (Denmark), 14002 (US), 14011 (US), 14045 (US), 14070 (US)

Enoxaparin cases:

- 2 critical organ bleeding: 1 subdural hematoma- at clinical site 60010 (India) and 1 intraspinal/hemorrhagic puncture- at clinical site 60001 (India)
- 2 bleeding leading to re-operation- at clinical sites: 14010 (US) and 32007 (Mexico)

The fatal bleeding and adrenal bleeding were reported from 2 of 8 unreliable clinical sites identified by DSI in RECORD 4 study. These major bleeding events are considered to be important safety information of rivaroxaban and should be included in the rivaroxaban labeling.

The other AE profiles are similar with or without RECORD 4 (see table below).

Summary of Adverse Events
(Subjects Valid for Safety Analysis in Pooled RECORD 1-3 Studies)

Preferred Term	**Rivaroxaban (N=4657)**	**Enoxaparin (N=4692)**
Any AEs	**2957 (63.5%)**	**3090 (65.9%)**
Any SAEs	**326 (7.0%)**	**422 (9.0%)**
Any death	**7 (0.2%)**	**19 (0.4%)**
Any adverse event resulting in permanent discontinuation of study drug	**170 (3.7%)**	**220 (4.7%)**
AEs occurred >1%		
Nausea	517 (11.1%)	519 (11.0%)
Pyrexia	400 (8.6%)	406 (8.7%)
Vomiting	452 (9.7%)	482 (10.3%)
Constipation	318 (6.8%)	335 (7.1%)
Hypotension	218 (4.7%)	215 (4.6%)
Peripheral edema	193 (4.1%)	162 (3.5%)
Anemia	192 (4.1%)	196 (4.2%)
Anemia postoperative	174 (3.7%)	167 (3.6%)
Procedural pain	158 (3.4%)	159 (3.4%)
Insomnia	158 (3.4%)	167 (3.6%)

Dizziness	151 (3.2%)	143 (3.1%)
Wound secretion	129 (2.8%)	93 (2.0%)
Hemoglobin decreased	112 (2.4%)	134 (2.9%)
ALT increased	113 (2.4%)	139 (3.0%)
Headache	108 (2.3%)	107 (2.3%)
Diarrhea	105 (2.3%)	137(2.9%)
Pruritus	97 (2.1%)	79 (1.7%)
AST increased	91 (2.0%)	112 (2.4%)
GGT increased	83 (1.8%)	126 (2.7%)
Urinary tract infection	82 (1.8%)	90 (1.9%)
Urinary retention	84 (1.8%)	84 (1.8%)
Pain in extremity	76 (1.6%)	55 (1.2%)
Arthralgia	63 (1.4%)	80 (1.7%)
Blister	67 (1.4%)	43 (0.9%)
Syncope	56 (1.2%)	32 (0.7%)
Hypertension	56 (1.2%)	67 (1.4%)
Muscle spasms	54 (1.2%)	32 (0.7%)
Tachycardia	53 (1.1%)	56 (1.2%)
Hematoma	50 (1.1%)	59 (1.3%)
Abdominal pain upper	49 (1.1%)	38 (0.8%)
Rash	50 (1.1%)	48 (1.0%)
Procedure hypotension	47 (1.0%)	34 (0.7%)
Wound hemorrhage	48 (1.0%)	44 (0.9%)

The liver toxicity of rivaroxaban was evaluated in long-term clinical studies for prevention of stroke in patients with atrial fibrillation (warfarin as comparator), for treatment of VTE in patients with symptomatic VTE (enoxaparin/VKA as comparator), and in patients with acute coronary syndrome (placebo as comparator in a phase 2 study). Overall, ALT >3 xULN was reported at a similar rate (2.5%) in the rivaroxaban group as compared to the comparator (2.3%) in the pooled analysis. The incidence of ALT abnormalities at different threshold (>5 xULN, 8 xULN, >10 xUN or >20 xULN) was similar between the rivaroxaban and the comparators. The overall incidence of ALT >3 x ULN with total bilirubin >2 x ULN in the rivaroxaban group (0.30%) was also comparable with the comparator (0.36%) in those long-term clinical studies. The overall incidence of reported hepatic adverse events and serious hepatic adverse events were similar between the rivaroxaban and the comparators in those trials. The overall number of cases with ALT >3 x ULN and total bilirubin >2 x ULN assessed to be possibly or probably related to the study drug was comparable in both treatment groups by an independent hepatic event assessment committee (HEAC) (0.03% vs. 0.01% by all 3 reviewers, 0.06% vs. 0.05% by at least 2 reviewers, and 0.11% vs. 0.13% by at least 1 review). No cases were considered to be definitely related to the study drug. In most rivaroxaban cases considered to be possibly related to rivaroxaban treatment, the events were resolved between 1 week and 2 months after rivaroxaban discontinued and in few cases the events resolved while rivaroxaban was continued. One patient with pulmonary embolism experienced ALT >3 x ULN with total bilirubin >2 x ULN and died 8 days later due to heart failure. All 3 HEAC reviewers considered the case as

possibly related to rivaroxaban treatment but all identified right-sided heart failure/shock liver as possible alternate etiology of the liver event.

Rivaroxaban has been approved in Canada and Europe for prophylaxis of VTE in patients undergoing hip or knee replacement surgery since September 2008. Post-marketing spontaneous reports between September 2008 and September 2010 reported 122 liver events in 66 patients and 88 serious liver events in 57 patients in an estimated 453,000 exposed patients. The most frequently reported hepatic events were the jaundice (12 cases), followed by colestasis (5 cases), and cytolytic hepatitis (4 cases). The most frequently reported investigation events were the transaminases increased (18 cases), followed by LFT abnormal (17 cases) and GGT increased (13 cases). HEAC reviewed 22 cases that met HEAC case criteria and considered the majority of cases as possibly or probably related to rivaroxaban treatment (10 by at least 2 reviewers and 8 by 1 reviewer). The time from the first rivaroxaban dose to event onset was 1 week or less in 26 cases, between 1 and 2 months in 3 cases, 100 days in 1 case, and not provided in 20 cases. Among the 66 cases, rivaroxaban was discontinued in 48 cases, continued in 1 case, not provided in 17 cases. The event was resolved in 27 cases (including the case in which rivaroxaban was continued), resolving in 18 cases, not resolved at the time of the report in 3 cases, not provided 18 cases. One case (201018977GPV) had a fatal outcome, however the outcome of the hepatic events was reported as resolving and the death was not attributed to any hepatic event. This case described a 76-year-old male patient who developed granulomatous liver disease in the context of pulmonary sarcoidosis 7 weeks after the last dose of rivaroxaban. Death was attributed to sepsis, acute respiratory distress syndrome (ARDS), and multiorgan failure.

Other significant adverse events reported associated with rivaroxaban treatment in post-marketing spontaneous reports were cerebral hemorrhage, epidural hematoma, hypersensitivity reactions including anaphylactic shock, agranulocytosis, and Steven-Johnson syndrome.

7.1 Methods

For the resubmission, long-term liver safety data from the recently completed phase 3/2 studies and ongoing phase 3 studies for other indications are reviewed. The important liver safety events are summarized by study and pooled to evaluate the overall liver safety for this product. The post-marketing data in other countries were reviewed for hepatic events and also for other important events.

The applicant has also provided ischemic stroke data from the long-term studies per the Agency's request during the review and the data are reviewed for safety.

7.1.1 Clinical Trials Used to Evaluate Safety

The submitted liver safety data included recently completed phase 2 and 3 studies, ongoing phase 3 studies, and post-marketing surveillance study and spontaneous reports since the Agency's CR letter. The Table below lists the recently completed phase 2 and 3 studies and ongoing phase 3 studies.

Recently Completed and Ongoing Clinical Studies

Study Name Study Number	Study Design	Comparator	Rivaroxaban Total Daily Dose	Scheduled Treatment Duration	Safety Population (N/total planned enrollment)
Completed Studies					
Phase 3 studies					
Atrial fibrillation					
ROCKET 39039039AFL3001 BAY59-7939/11630	Double-blind, active-controlled	Warfarin	20 mg/15 mg[a]	Chronic (up to 4 yrs.)	14,236/ 14,000
J [Japan]-ROCKET BAY59-7939/12620	Double-blind, active-controlled	Warfarin	15 mg/10 mg[b]	Chronic (up to 2.5 yrs.)	1,278/ 1,200
VTE Treatment					
EINSTEIN Extension BAY59-7939/11899	Double-blind, placebo-controlled	Placebo	20 mg	6 or 12 months	1,188[c]/ 1,300
EINSTEIN DVT BAY59-7939/11702	Open label, active-controlled	Enoxaparin/ VKA	30 mg for 3 weeks; then 20 mg	3, 6, or 12 months	3,429/ 2,900
Phase 2 studies					
ATLAS ACS TIMI 46 39039039ACS2001 BAY59-7939/11898 Patients with acute coronary syndrome	Double-blind, placebo-controlled	Placebo	5, 10, 15, and 20 mg	6 months	3,462/ 3600
ODIXa-DVT BAY59-7939/11223 Patients with DVT	Open label, active-controlled	Enoxaparin/ VKA	20, 40, and 60 mg	12 weeks	604
Einstein-DVT; EINSTEIN BAY59-7939/11528 Patients with DVT	Open label, active-controlled	Heparin or LMWH /VKA	20, 30, and 40 mg	12 weeks	542
Ongoing Studies					
Phase 3 studies					
EINSTEIN PE BAY59-7939/11702 Patients with PE	Open label, active-controlled	Enoxaparin/ VKA	30 mg for 3 weeks; then 20 mg	3, 6, or 12 months	4,003/ 4,400[d]
ATLAS ACS 2 TIMI 51 39039039ACS3001 BAY59-7939/13194 Patients with acute coronary syndrome	Double-blind, placebo-controlled	Placebo	5 and 10 mg	Chronic (up to 2.5 yrs.)	12,705/ 14,500[e]
MAGELLaN BAY59-7939/12839 DVT prophylaxis in	Double-blind, active-controlled	Enoxaparin/ Placebo	10 mg	35 days	8,097/ ~8,000 [d]

medical patients					

Note: ACS = acute coronary syndrome; DVT = deep venous thrombosis; PE = pulmonary embolism; TIMI = thrombolysis in myocardial infarction; VKA = vitamin K antagonist; VTE= venous thromboembolism; LMWH = low molecular weight heparin; N/A = not applicable; THR = total hip replacement; TIMI = thrombolysis in myocardial infarction; TKR = total knee replacement; VTE = venous thromboembolism
a In ROCKET, subjects with moderate renal impairment on entry to the study received 15 mg rivaroxaban.
b In J-ROCKET, subjects with moderate renal impairment on entry to the study received 10 mg rivaroxaban.
c In EINSTEIN Extension, 632 subjects valid for safety were previously enrolled in EINSTEIN DVT/PE.
d Safety data from these ongoing studies are presented as of last subject visit cutoff date of 15 September 2010.
e Safety data from ATLAS ACS 2 TIMI 51 are presented as of last subject visit cutoff date of 13 September 2010.

7.1.2 Categorization of Adverse Events

Liver safety evaluation focused on the following assessments:
- ALT abnormalities
- ALT >3xULN and total bilirubin >2xULN
- Hepatic disorder AEs
- Causality assessment for potential serious liver events

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The liver safety data from long-term studies in different populations were evaluated individually and also pooled for overall liver safety assessment.

7.2 Adequacy of Safety Assessments

The submitted liver safety data and assessment are adequate. In submitted clinical trials, over 14,000 patients were exposed to rivaroxaban with over 7,000 patients having mean treatment duration of about 1.5 years. See the Table below for the rivaroxaban dose, treatment duration and exposed number of patients in the clinical trials.

Rivaroxaban Dosage and Treatment Duration in Clinical Studies

Study Name Study Number	Protocol-defined Dose(s)	Rivaroxaban Safety Population N	Days of Treatment	
			Mean ± SD	Min, Max
ROCKET 39039039AFL3001	20 mg/ 15 mga	7111	572.2 ± 294.7	1 - 1263
J-ROCKET BAY59-7939/12620	15 mg/ 10 mgb	639	498.9 +/- 219.0	1 – 868
EINSTEIN Extension BAY 59-7939/11899	20 mg	598 e	189.5 ± 85.1	4 - 372

EINSTEIN DVT BAY59-7939/11702 DVT	30 mg/ 20 mgf	1718	194.4 ± 89.7	1 - 401
EINSTEIN PE BAY59-7939/11702 PE	30 mg/ 20 mgf	2011	195.6 ± 100.7	1 - 397
ATLAS ACS 2 TIMI 46 39039039ACS2001	5 mg, 10 mg, 20 mg	2309	159.1 ± 52.4	1 - 228

Subject years of exposure to each treatment group in the clinical studies are shown below. The total subject years of exposure for rivaroxaban is 15,507 with over 70% of this exposure coming from the ROCKET study individually (11,141/15,507=72%) and over 75% from the combined atrial fibrillation studies (12,013/15,507=77%).

Table 2.1-1: Subject years of exposure

Study	Rivaroxaban	Comparator
ROCKET	11140.7	11311.4
J-ROCKET	872.7	841.6
EINSTEIN DVT	914.4	881.6
EINSTEIN PE	1076.9	1050.9
EINSTEIN Extension	308.2	304.5
ATLAS ACS TIMI 46	1005.5	516.4
ODIXa-DVT (11223)	100.9	26.8
EINSTEIN (11528)	87.7	30.1
Total	15507	14963

Liver-related laboratory assessment conducted in clinical trials:

- ROCKET and J-ROCKET: baseline, at 2 and 4 weeks, then monthly to 1 year, every 3 months thereafter
- EINSTEIN DVT, PE and Extension: Baseline, at Day 15 and 30, then monthly thereafter
- ATLAS ACS 2 TIMI 46: Baseline, at Day 1 and 7, Day 30, then monthly thereafter

7.3 Liver Safety Data in Long-term Clinical Studies

7.3.1 ALT abnormalities

Rocket and J-Rocket Studies

In the ROCKET study ALT elevations in all categories were comparable between the rivaroxaban and warfarin treatment groups (see table below). In J-Rocket study, a few more subjects in the rivaroxaban group had ALT> 5 xULN and >8 xULN as compared to the warfarin group.

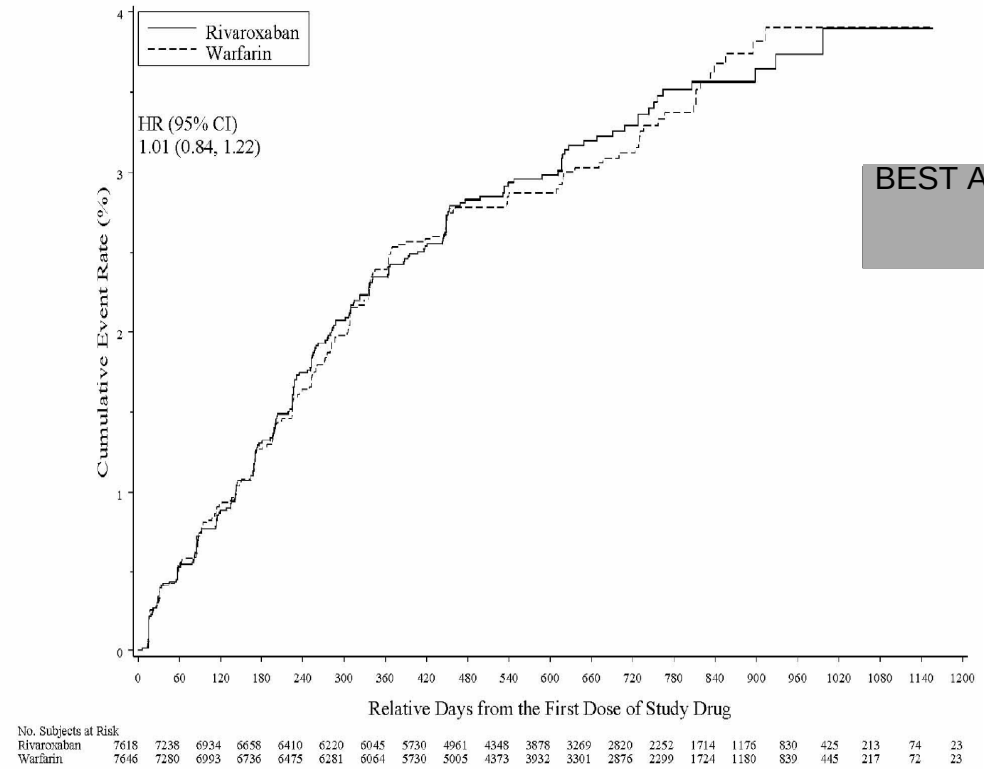
Incidence of post-baseline ALT Abnormalities in ROCKET (central lab) and J-Rocket Studies (local lab)

Studies	ALT Criteria	Rivaroxaban (N=7111) n/N (%)	Warfarin (N=7125) n/N (%)	HR Rivaroxaban to warfarin (95% CI)
Rocket	> 3 X ULN	203/6979(2.91)	203/7008(2.90)	1.01(0.83,1.23)
	> 5 X ULN	72/6979(1.03)	68/7008(0.97)	1.07(0.77,1.49)
	> 8 X ULN	27/6979(0.39)	28/7008(0.40)	0.97(0.57,1.65)
	> 10 X ULN	17/6979(0.24)	20/7008(0.29)	0.86(0.45,1.64)
	> 20 X ULN	3/6979(0.04)	4/7008(0.06)	
J-Rocket	> 3 X ULN	14/639(2.19)	14/638(2.19)	0.98(0.47,2.05)
	> 5 X ULN	9/639(1.41)	3/638(0.47)	2.93(0.79,10. 84)
	> 8 X ULN	6/639(0.94)	1/638(0.16)	
	> 10 X ULN	2/639(0.31)	1/638(0.16)	
	> 20 X ULN	0	0	
Pooled	> 3 X ULN	217/7618(2.85)	217/7646(2.84)	1.01(0.84,1.22)
	> 5 X ULN	81/7618(1.06)	71/7646(0.93)	1.15(0.84,1.58)
	> 8 X ULN	33/7618(0.43)	29/7646(0.38)	1.15(0.70,1.89)
	> 10 X ULN	19/7618(0.25)	21/7646(0.27)	0.91(0.49,1.70)
	> 20 X ULN	3/7618(0.04)	4/7646(0.05)	

ULN = Upper Limit of Normal Range
POST BASELINE: Uses the lab value after the first study dose date.
n = Number of subjects with events.
N = Number of subjects with non-missing baseline lab values (for BASELINE), with non-missing post baseline lab values (for POST BASELINE).
Hazard Ratio (95% CI): time to event analysis using a Cox model stratified by study with treatment as the covariate. Hazard ratio will be provided when the total number of events is 10 or more for the two treatment groups combined and at least 1 event occurs in each group

The cumulative incidence over time to the first post-baseline ALT >3x ULN for the pooled ROCKET and J-ROCKET atrial fibrillation studies has a similar pattern for both the rivaroxaban and the warfarin groups (see Figure below). At Day 180 the cumulative incidence was 1.31% for rivaroxaban and 1.27% for warfarin, while at Day 360 the rates were 2.34% and 2.39%, respectively.

Figure 2.1-1: Kaplan-Meier Plot of Time from the First Study Medication Administration to the First Postbaseline ALT > 3xULN for Pooled ROCKET and J-ROCKET studies (Based on Central Lab for ROCKET and local lab for J-ROCKET)



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Note: Hazard ratio (95% CI) of Rivaroxaban versus Warfarin from the Cox proportional hazard model with treatment as a covariate.
Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.
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VTE Treatment Studies

In EINSTEIN DVT and PE studies, enoxaparin was used in the initial treatment period in the comparator groups. Analyses were done both including all events after randomization and including only events that occurred after Day 21 in both treatment groups in order to compare ALT abnormalities between rivaroxaban and the VKA (primarily warfarin but acenocoumarol also allowed) only dosing period (see table below). When all events were included in these two studies, rivaroxaban had a lower incidence of ALT >3x ULN and ALT >5x ULN as compared to comparator while the incidence of ALT >8x ULN and >10x ULN showed a similar trend between the two groups. When only ALT elevations occurring after Day 21 were included in the analysis similar rates of ALT abnormalities between the rivaroxaban and comparator groups were seen in the EINSTEIN DVT study but a slightly higher rate of ALT abnormalities was seen in the rivaroxaban group as compared to the comparator in the EINSTEIN PE study.

In the EINSTEIN Extension study, there was an increased number of cases with rivaroxaban for ALT >3 xULN as compared to the placebo control. About 50% of the subjects in the EINSTEIN Extension study previously participated in either the EINSTEIN DVT or PE studies.

Incidence of post-baseline ALT Abnormalities in VTE Phase 2/3 treatment studies (Based on Central Lab)

Studies	ALT Criteria	Rivaroxaban n/N (%)	Comparators[a] n/N (%)	HR Rivaroxaban to warfarin (95% CI)
EINSTEIN DVT (completed)				
All events	> 3 X ULN	25/1680 (1.5)	62/1649 (3.8)	0.39 (0.24, 0.62)
	> 5 X ULN	6/1680 (0.4)	18/1649 (1.1)	0.32(0.13, 0.81)
	> 8 X ULN	4/1680 (0.2)	7/1649 (0.4)	0.55 (0.16, 1.89)
	> 10 X ULN	3/1680 (0.2)	3/1649 (0.2)	
	> 20 X ULN	0	0	
Events occurring after Day 21	> 3 X ULN	20/1662 (1.2)	23/1618 (1.4)	0.84 (0.46, 1.52)
	> 5 X ULN	6/1662 (0.4)	5/1618 (0.3)	1.15 (0.35, 3.77)
	> 8 X ULN	4/1662 (0.2)	2/1618 (0.1)	
	> 10 X ULN	3/1662 (0.2)	1/1618 (0.1)	
	> 20 X ULN	0	0	
EINSTEIN PE (ongoing)				
All events	> 3 X ULN	33/1876 (1.8)	49/1840 (2.7)	0.65 (0.42, 1.02)
	> 5 X ULN	9/1876 (0.5)	15/1840 (0.8)	0.59 (0.26, 1.34)
	> 8 X ULN	4/1876 (0.2)	2/1840 (0.1)	
	> 10 X ULN	2/1876 (0.1)	2/1840 (0.1)	
	> 20 X ULN	0	0	
Events occurring after Day 21	> 3 X ULN	24/1825 (1.3)	7/1786 (0.4)	3.37 (1.45, 7.82)
	> 5 X ULN	7/1825 (0.4)	2/1786 (0.1)	
	> 8 X ULN	4/1825 (0.2)	1/1786 (0.1)	
	> 10 X ULN	2/1825 (0.1)	1/1786 (0.1)	
	> 20 X ULN	0	0	
EINSTEIN Extension (completed)				
All events	> 3 X ULN	11/591 (1.9)	3/586 (0.5)	3.56 (0.99,12.8)
	> 5 X ULN	2/591 (0.3)	0	
	> 8 X ULN	1/591 (0.2)	0	
	> 10 X ULN	1/591 (0.2)	0	
	> 20 X ULN	0	0	
Pooled Phase 2/3 studies (completed and ongoing)				
All events	> 3 X ULN	78/4415(1.77)	137/3740(3.66)	0.41(0.31,0.55)
	> 5 X ULN	20/4415(0.45)	45/3740(1.20)	0.30(0.17,0.52)
	> 8 X ULN	10/4415(0.23)	13/3740(0.35)	0.54(0.23,1.27)
	> 10 X ULN	6/4415(0.14)	7/3740(0.19)	0.63(0.20,1.94)

	> 20 X ULN	1/4415(0.02)	0	
Events occurring after Day 21	> 3 X ULN	69/4910(1.41)	36/4235(0.85)	1.60(1.07,2.41)
	> 5 X ULN	20/4910(0.41)	7/4235(0.17)	2.34(0.98,5.61)
	> 8 X ULN	11/4910(0.22)	3/4235(0.07)	3.14(0.87,11.37)
	> 10 X ULN	7/4910(0.14)	2/4235(0.05)	
	> 20 X ULN	1/4910(0.02)	0	

a Comparators: All events: Enoxaparin/VKA, (LMW) Heparin/VKA; Events occurring after Day 21: Enoxaparin/VKA, (LMW) Heparin/VKA or Placebo.
ULN = Upper Limit of Normal Range
POST BASELINE: Uses the lab value after the first study dose date.
N = Number of subjects with non-missing baseline lab values (for BASELINE), with non-missing post baseline lab values (for POST BASELINE).
Hazard Ratio (95% CI): time to event analysis using a Cox model stratified by study with treatment as the covariate. Hazard ratio will be provided when the total number of events is 10 or more for the two treatment groups combined and at least 1 event occurs in each group

ACS (acute coronary syndrome) study

For the Phase 2 ATLAS ACS TIMI 46 study ALT elevations at all thresholds were lower for rivaroxaban compared with placebo. However, most patients in the placebo group received heparin/LWM heparin early for the management of ACS.

Incidence of post-baseline ALT Abnormalities in Phase 2 ATLAS ACS TIMI 46 study

ALT Criteria	Rivaroxaban n/N (%)	Placebo n/N (%)
> 3 X ULN	85/2270 (3.7)	52/1133 (4.6)
> 5 X ULN	18/2270 (0.8)	16/1133 (1.4)
> 8 X ULN	4/2270 (0.2)	4/1133 (0.4)
> 10 X ULN	3/2270 (0.1)	3/1133 (0.3)
> 20 X ULN	0	0

Overall Pooled Analysis

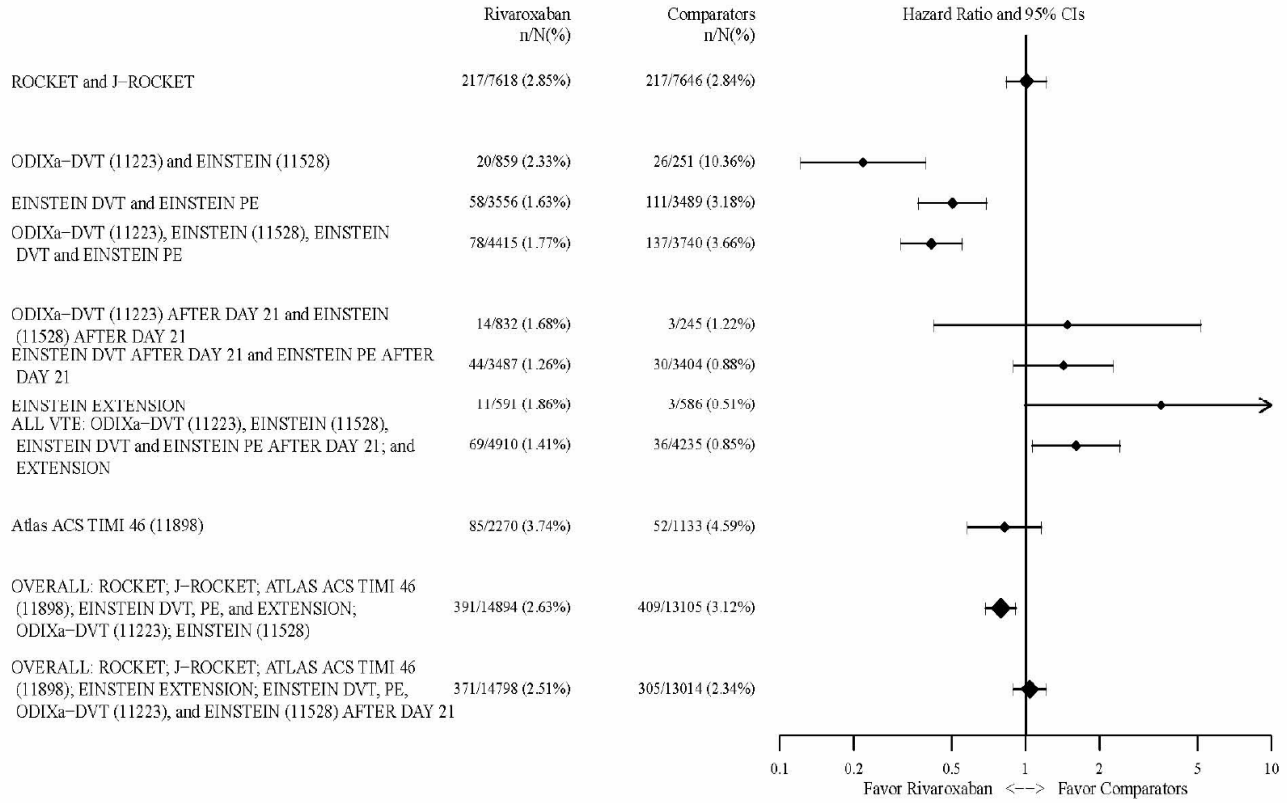
After excluding the events occurring before Day 21 in the VTE treatment studies, slightly higher rates of ALT >3x ULN, >5x ULN and ALT >8x ULN were seen with rivaroxaban than with VKA or placebo. However, the difference between the two groups is within 0.2%.

Incidence of Post-baseline ALT Laboratory Abnormalities with Hazard Ratios (Based on Central Lab, except for J-Rocket) in Pooled ROCKET; J-ROCKET; EINSTEIN DVT AND PE AFTER DAY 21; EINSTEIN Extension; ODIXa-DVT AFTER DAY 21; EINSTEIN AFTER DAY 21; and ATLAS ACS TIMI 46 Studies

ALT Abnormalities		Rivaroxaban (N=15262) n/J(%)	Warfarin (N=13469) n/J(%)	HR Rivaroxaban to comparators (a) (95% CI)
ALT	> 3 X ULN	371/14798(2.51)	305/13014(2.34)	1.04(0.89,1.21)
	> 5 X ULN	119/14798(0.80)	94/13014(0.72)	1.12(0.85,1.47)
	> 8 X ULN	48/14798(0.32)	36/13014(0.28)	1.22(0.79,1.89)
	> 10 X ULN	29/14798(0.20)	26/13014(0.20)	1.02(0.60,1.74)
	> 20 X ULN	4/14798(0.03)	4/13014(0.03)	

The following Figure summarizes ALT >3 x ULN in each study and in pooled analysis. Overall, the rate of ALT >3 x ULN with rivaroxaban was similar to that with the comparators in the pooled analysis.

Figure 2.1-2: Hazard Ratio for Time from the First Study Drug Administration to the First Postbaseline ALT > 3xULN (Based on Central Lab except for J–ROCKET) for Phase 2 and Phase 3 Studies (Safety Analysis Set)



Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.
Note: Symbol size is proportional to the number of events.
Note: Arrow (< or >) of a line indicates that the confidence interval limit exceeds the X–axis range.

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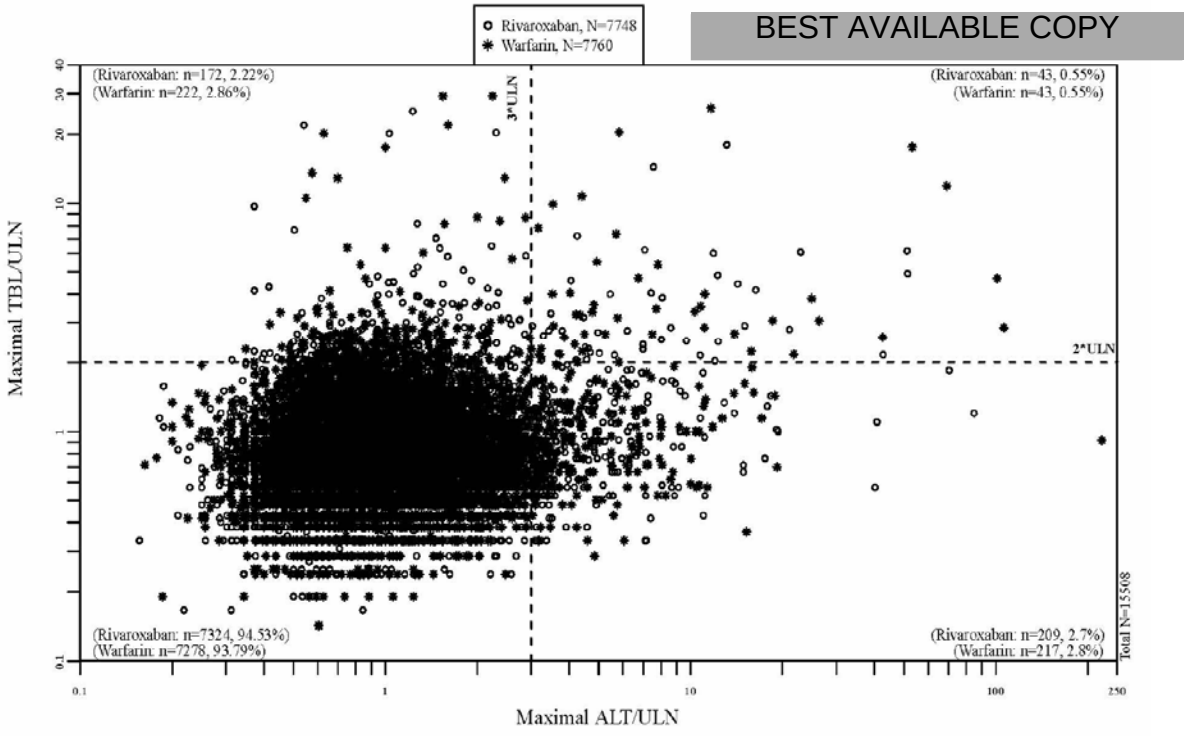
7.3.2 **ALT >3xULN and total bilirubin >2xULN (potential Hy's law cases)**

ROCKET and J-ROCKET studies

An plot of maximal ALT levels by maximal total bilirubin levels at any time for the pooled ROCKET and J-ROCKET studies is shown in Figure below. As shown in the right upper quadrant of the eDISH plot, 43 (0.55%) subjects in each treatment group had elevations in ALT and total bilirubin that met the thresholds of >3xULN and >2xULN, respectively. The right lower quadrant reflecting ALT >3x ULN elevations without total bilirubin >2x ULN elevations was also comparable between the treatment groups (rivaroxaban 209/7748=2.7%, warfarin 217/7760=2.8%).

Figure 2.1-3: Scatter Plot of Baseline and Postbaseline Maximum ALT Levels with Maximum Total Bilirubin Levels (Based on Central and Local Labs)
ROCKET and J-ROCKET: Safety Analysis Set



In the ROCKET study, the number of combined maximal ALT levels >3x ULN with maximal total bilirubin levels >2x ULN cases at any time including both central and local laboratory data was 39 (0.55%) in each rivaroxaban and warfarin treatment group. This includes all cases regardless of the order of the elevations (e.g., either the ALT or the total bilirubin elevation could occur first) and of the timing of the elevations in relation to each other.

Six rivaroxaban subjects and 4 warfarin subjects had the total bilirubin elevation occur either first or more than 30 days after the ALT elevation. These subjects were not considered potential serious liver cases and were not sent for causality assessment.

The number of cases with post-baseline concurrent and/or non-concurrent with the ALT elevation first followed by the total bilirubin elevation within 30 days, which are considered to be potential Hy's law cases, was similar between the rivaroxaban and warfarin treatment groups (rivaroxaban n=33, warfarin n=35) (see Table below).

In the pooled ROCKET and J-ROCKET atrial fibrillation studies, the number of post-baseline combined concurrent (occurred on the same day) ALT >3x ULN with total bilirubin >2x ULN cases was 34 (0.45%) with rivaroxaban and 36 (0.47%) with warfarin).

The total number of combined concurrent and non-concurrent (the ALT elevation occurred first followed by the total bilirubin elevation within the following 30 days) cases was 36 (0.47%) for rivaroxaban and 38 (0.50%) for warfarin. The number of cases with direct bilirubin 50% or higher was also comparable between the treatment groups.

Incidence of Post-baseline Combined ALT > 3xULN and Total Bilirubin > 2xULN in ROCKET (central and local labs) and J-Rocket (local labs) Studies

ALT/TBL (BILIDIR)		Rivaroxaban n/N(%)	Warfarin n/N(%)	HR Rivaroxaban to warfarin (95% CI)
Rocket Study				
ALT >3 x ULN and TBL > 2 x ULN	Concurrent and non-concurrent cases	33/6980 (0.47)	35/7012 (0.50)	0.96(0.59,1.54)
	Concurrent (same day)	31/6980 (0.44)	33/7012 (0.47)	0.95(0.58,1.55)
	Non-concurrent (ALT followed by TBL within 30 days)	21/6980 (0.30)	22/7012 (0.31)	0.97(0.53,1.76)
ALT>3 xULN, TBL>2 x ULN and BILIDIR ≥ 0.5 TBL	Concurrent and non-concurrent cases	13/6975 (0.19)	19/7000 (0.27)	0.76(0.39,1.48)
	Concurrent (same day)	9/6975 (0.13)	9/7000 (0.13)	0.69(0.34,1.40)
	Non-concurrent (ALT followed by TBL within 30 days)	15/6975 (0.22)	20/7000 (0.29)	1.01(0.40,2.55)
J-Rocket Study				
ALT >3 x ULN and TBL > 2 x ULN	Concurrent and non-concurrent cases	3/638(0.47)	3/638(0.47)	
	Concurrent (same day)	3/638(0.47)	3/638(0.47)	
	Non-concurrent (ALT followed by TBL within 30 days)	1/638(0.16)	3/638(0.47)	
ALT>3 xULN, TBL>2 x ULN and BILIDIR ≥ 0.5 TBL	Concurrent and non-concurrent cases	3/638(0.47)	3/638(0.47)	
	Concurrent (same day)	3/638(0.47)	3/638(0.47)	
	Non-concurrent (ALT followed by TBL within 30 days)	1/638(0.16)	2/638(0.31)	
Pooled Rocket and J-Rocket studies				
ALT >3 x ULN and	Concurrent and non-	36/7618(0.47)	38/7650(0.50)	0.96(0.61,1.51)

TBL > 2 x ULN	concurrent cases			
	Concurrent (same day)	34/7618(0.45)	36/7650(0.47)	0.95(0.60,1.52)
	Non-concurrent (ALT followed by TBL within 30 days)	22/7618(0.29)	25/7650(0.33)	0.89(0.50,1.58)
ALT>3 xULN, TBL>2 x ULN and BILIDIR ≥ 0.5 TBL	Concurrent and non-concurrent cases	18/7613(0.24)	23/7638(0.30)	0.79(0.43,1.46)
	Concurrent (same day)	16/7613(0.21)	22/7638(0.29)	0.73(0.38,1.40)
	Non-concurrent (ALT followed by TBL within 30 days)	10/7613(0.13)	11/7638(0.14)	0.92(0.39,2.16)

POST BASELINE: After the first study medication date for subjects with non-missing post baseline values
BILIDIR: direct bilirubin
ULN = Upper Limit of Normal Range; TBL: TOTAL BILIRUBIN; BILIDIR: DIRECT BILIRUBIN;
n = Number of subjects with events; J= Number of subjects with non-missing ALT and TBL lab values for concurrent and/or non-concurrent cases for each time period
Hazard Ratio (95% CI): time to event analysis of the first ALT>3xULN and TBL>2xULN was done for subjects having combined cases using a Cox model with the treatment as the covariate. Hazard ratio will be provided for post baseline and treatment emergent concurrent cases and postbaseline concurrent and non-concurrent cases, when a total number of events is greater than 10 for two treatment groups and at least 1 event in both groups.

VTE Treatment Studies

There were 9 cases with combined ALT > 3xULN and total bilirubin > 2xULN in the rivaroxaban patients as compared to 6 cases in the VTE treatment studies. There were fewer cases with combined ALT > 3xULN and total bilirubin > 2xULN in EINSTEIN DVT study but a few more cases in EINSTEIN PE study in the rivaroxaban group as compared to the comparators. Two additional cases were in phase 2 studies in the rivaroxaban group; however, the number of patients in the rivaroxaban group was 3 times more than that in the comparator group in those phase 2 studies.

The EINSTEIN Extension study did not have any combined ALT > 3xULN with total bilirubin > 2xULN cases in either treatment group.

Incidence of Post-baseline Combined ALT > 3xULN and Total Bilirubin > 2xULN in VTE Treatment (central and local labs) Studies (ODIXa-DVT, EINSTEIN, EINSTEIN DVT AND EINSTEIN PE)

ALT/TBL (BILIDIR)		Rivaroxaban n/N(%)	Comparator[a] n/N(%)	HR Rivaroxaban to warfarin (95% CI)
EINSTEIN DVT Study				
ALT >3 x ULN and TBL > 2 x ULN	Concurrent and non-concurrent cases	2/1682 (0.1)	4/1649 (0.2)	
	Concurrent (same day)	2/1682 (0.1)	4/1648 (0.2)	
	Non-concurrent (ALT followed by TBL within 30 days)	2/1642 (0.1)	3/1585 (0.2)	
ALT>3 xULN, TBL>2 x ULN and BILIDIR ≥ 0.5 TBL	Concurrent and non-concurrent cases	1/1677 (0.1)	2/1639 (0.1)	
	Concurrent (same day)	1/1677 (0.1)	2/1639 (0.1)	

	Non-concurrent (ALT followed by TBL within 30 days)	1/1632 (0.1)	1/1558 (0.1)	
EINSTEIN PE Study				
ALT >3 x ULN and TBL > 2 x ULN	Concurrent and non-concurrent cases	5/1880 (0.3)	2/1841 (0.1)	
	Concurrent (same day)	4/1878 (0.2)	2/1839 (0.1)	
	Non-concurrent (ALT followed by TBL within 30 days)	5/1801 (0.3)	2/1744 (0.1)	
ALT>3 xULN, TBL>2 x ULN and BILIDIR ≥ 0.5 TBL	Concurrent and non-concurrent cases	2/1877 (0.1)	0/ 1833 (0.0)	
	Concurrent (same day)	2/1877 (0.1)	0/ 1726 (0.0)	
	Non-concurrent (ALT followed by TBL within 30 days)	1/1780 (0.1)	0/ 1833 (0.0)	
ODIXa-DVT (11223) and EINSTEIN (11528)				
ALT >3 x ULN and TBL > 2 x ULN	Concurrent and non-concurrent cases	2/859 (0.23)	0/251 (0.0)	
	Concurrent (same day)	1/859 (0.12)	0/251 (0.0)	
	Non-concurrent (ALT followed by TBL within 30 days)	2/566 (0.35)	0/157 (0.0)	
Pooled VTE Treatment Studies				
ALT >3 x ULN and TBL > 2 x ULN	Concurrent and non-concurrent cases	9/4421 (0.20)	6/3741 (0.16)	1.28 (0.45,3.64)
	Concurrent (same day)	7/4419(0.16)	6/3738(0.16)	1.05(0.35,3.15)
	Non-concurrent (ALT followed by TBL within 30 days)	9/4009(0.22)	5/3486(0.14)	1.51(0.50,4.59)
ALT>3 xULN, TBL>2 x ULN and BILIDIR ≥ 0.5 TBL	Concurrent and non-concurrent cases	3/3554 (<0.1)	2/3472 (<0.1)	
	Concurrent (same day)	3/3554(<0.1)	2/3472(<0.1)	
	Non-concurrent (ALT followed by TBL within 30 days)	2/3412(<0.1)	1/3284(<0.1)	

Note: POST BASELINE: After the first study medication date for subjects with non-missing post baseline values BILIDIR
(a) Comparators: Enoxaparin/VKA, (LMW) Heparin/VKA.
ULN = Upper Limit of Normal Range; TBL: TOTAL BILIRUBIN; BILIDIR: DIRECT BILIRUBIN;
n = Number of subjects with events; N= Number of subjects with non-missing ALT and TBL lab values for concurrent and/or non-concurrent cases for each time period
POST BASELINE: After the first study medication date for subjects with non-missing post baseline values
Hazard Ratio (95% CI): time to event analysis using a Cox model stratified by study with treatment as the covariate pooling ODIXa-DVT (11223) and Einstein (11528). Hazard ratio will be provided when the total number of events is 10 or more for the two treatment groups combined and at least 1 event occurs in each group.

ACS study

There were no combined ALT > 3xULN and total bilirubin > 2xULN cases in the rivaroxaban group (0/2270, 0%) while there were 3 cases in the placebo group (3/1134, 0.26%).

Overall Pooled Analysis

The rate of combined ALT > 3xULN and total bilirubin > 2xULN was comparable between the rivaroxaban and the comparator groups in pooled analysis (see Table below). The overall number of cases was 45 (0.30%) for rivaroxaban and 47 (0.36%) for comparators with a pooled HR of 0.92 (95% CI 0.61, 1.39). The number of post-baseline cases with a direct bilirubin 50% or higher was also similar between the two groups.

Incidence of Post-baseline Combined ALT > 3xULN and Total Bilirubin > 2xULN (Based on Central and Local Labs)
In Pooled ROCKET; J-ROCKET; EINSTEIN DVT, PE, AND EXTENSION; ODIXa-DVT; EINSTEIN; AND ATLAS ACS TIMI 46 Studies

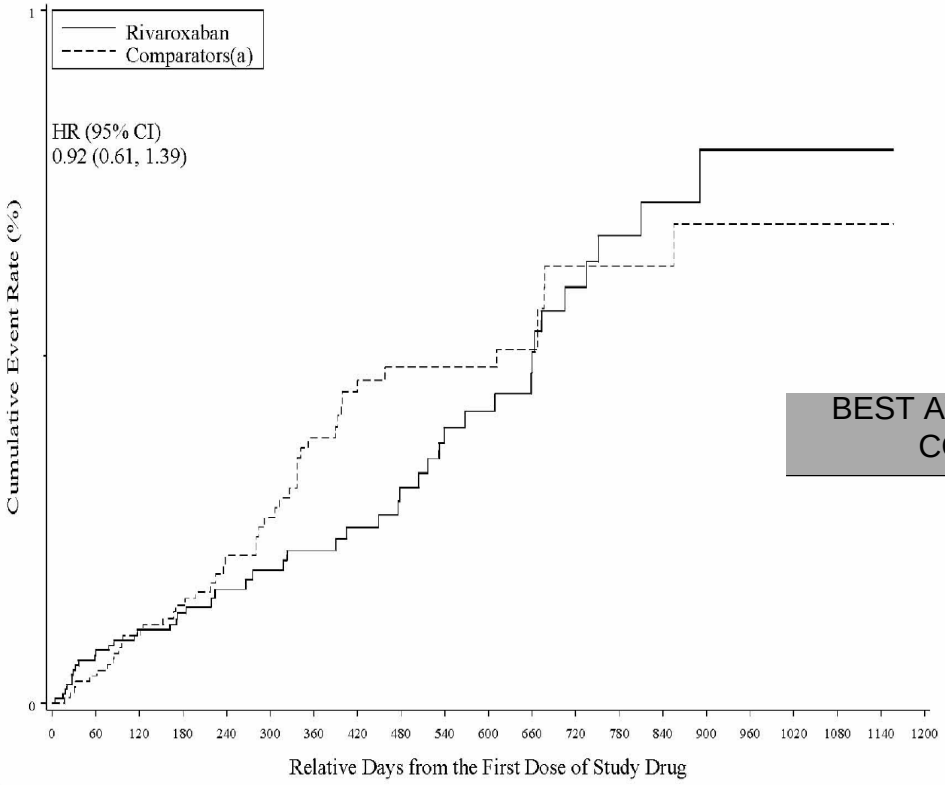
ALT/TBL (BILIDIR)		Rivaroxaban (N=15262) n/J(%)	Comparators(a) (N=13469) n/J(%)	HR Rivaroxaban to Comparators(a) (95% CI)
ALT >3 x ULN and TBL > 2 x ULN	Concurrent and non-concurrent cases	45/14899(0.30)	47/13111(0.36)	0.92(0.61,1.39)
	Concurrent (same day)	41/14897(0.28)	45/13108(0.34)	0.88(0.58,1.35)
	Non-concurrent (ALT followed by TBL within 30 days)	31/14471(0.21)	33/12848(0.26)	0.88(0.54,1.44)
ALT>3 xULN, TBL>2 x ULN and BILIDIR ≥ 0.5 TBL	Concurrent and non-concurrent cases	13/6975 (0.19)	19/7000 (0.27)	0.76(0.39,1.48)
	Concurrent (same day)	19/14024(0.14)	25/12827(0.19)	0.75(0.41,1.37)
	Non-concurrent (ALT followed by TBL within 30 days)	21/14024(0.15)	26/12827(0.20)	0.80(0.45,1.42)

POST BASELINE: After the first study medication date for subjects with non-missing post baseline values
BILIDIR: direct bilirubin
ULN = Upper Limit of Normal Range; TBL: TOTAL BILIRUBIN; BILIDIR: DIRECT BILIRUBIN;
n = Number of subjects with events; J= Number of subjects with non-missing ALT and TBL lab values for concurrent and/or non-concurrent cases for each time period
Hazard Ratio (95% CI): time to event analysis of the first ALT>3xULN and TBL>2xULN was done for subjects having combined cases using a Cox model with the treatment as the covariate. Hazard ratio will be provided for post baseline and treatment emergent concurrent cases and postbaseline concurrent and non-concurrent cases, when a total number of events is greater than 10 for two treatment groups and at least 1 event in both groups.

The following Kaplan-Meier figure shows the cumulative incidence of post-baseline ALT >3xULN with total bilirubin >2x ULN either on the same day or with the total bilirubin elevation within the following 30 days after the ALT elevation. At Day 180 the cumulative incidence was

0.13% for rivaroxaban and 0.14% for comparators, while at Day 360 the rates were 0.22% and 0.38%, respectively.

Figure 2.1-5: Kaplan-Meier Plot of Time from the First Study Medication Administration to the First Postbaseline Concurrent and Non-Concurrent ALT > 3xULN followed by Total Bilirubin > 2xULN within 30 Days (Based on Central and Local Labs)
ROCKET; J-ROCKET; EINSTEIN DVT, PE, and EXTENSION; ODIXa-DVT (11223); EINSTEIN (11528); and ATLAS ACS TIMI 46 (11898)



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No. Subjects at Risk

Rivaroxaban	14899	14098	12722	11718	7477	7150	6756	5847	5063	4434	3942	3336	2873	2294	1745	1200	846	431	213	74	23
Comparators(a)	13111	12418	11606	10718	7512	7178	6758	5848	5114	4465	4005	3368	2934	2355	1772	1212	859	457	222	73	23

(a) Comparators: WARFARIN, Enoxaparin VKA, (LMW) Heparin Vitamin K-antagonist or Placebo.
Note: Hazard ratio (95% CI) of Rivaroxaban versus Comparator from the Cox proportional hazard model stratified by study with treatment as a covariate pooling ODIXa-DVT (11223) and Einstein (11528), and pooling Einstein Extension and DVT.
Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.
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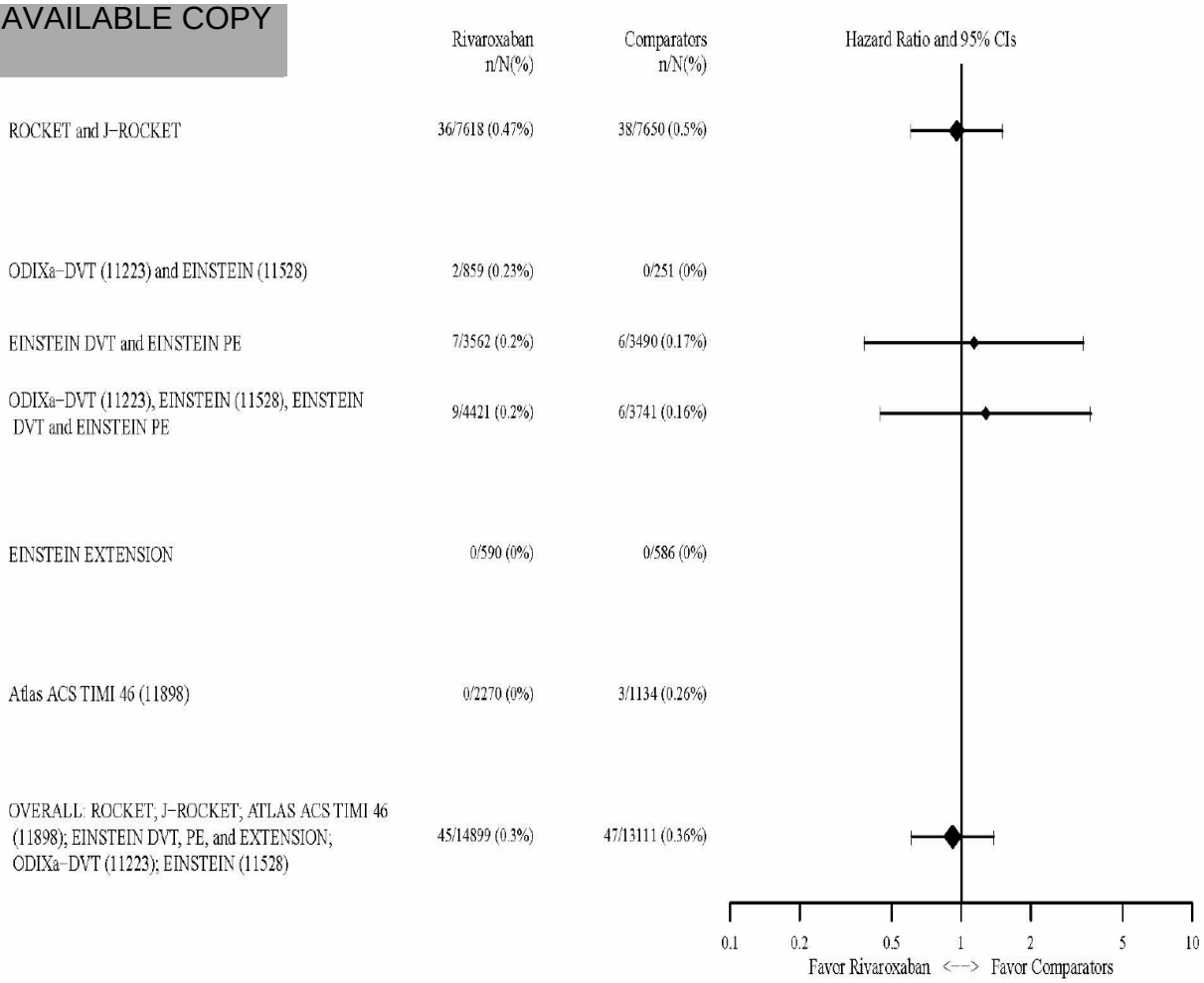
The following Figure summarizes the cases of post-baseline ALT >3xULN with total bilirubin >2x ULN either on the same day or with the total bilirubin elevation within the following 30 days after the ALT elevation in each and pooled studies. Overall, the rates of post-baseline concurrent and non-concurrent ALT >3xULN and total bilirubin >2x ULN were similar between the rivaroxaban treatment and the comparator treatment based on the pooled analysis.

Figure 2.1-4: Hazard Ratio for Time from the First Study Drug Administration to the First Postbaseline ALT > 3xULN followed by Total Bilirubin > 2x ULN either on the same day or within 30 Days (Based on Central and Local Labs) for Phase 2 and Phase 3 Studies: Safety Analysis Set



Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.
Note: Symbol size is proportional to the number of events.

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7.3.3 **Hepatic disorder AEs**

ROCKET and J-ROCKET Studies

The following table shows the post-baseline hepatic disorder adverse events reported in Rocket studies. The overall rate of hepatic adverse events (AEs), serious adverse events (SAEs) and AEs

leading to permanent study drug discontinuation identified by Standardized MedDRA Query (SMQ) was similar between the rivaroxaban and warfarin groups.

Post-baseline Hepatic Disorder Adverse Events
Based on Hepatic Disorder Standardized MedDRA Query

Hepatic Disorder	Rivaroxaban (N=7750)	Warfarin (N=7764)	Rivaroxaban Minus Warfarin Diff (%) 95% CI(%) (a)
Rocket Study			
AEs	421 (5.92)	657 (9.22)	-3.30 (-4.17, -2.43)
SAEs	69 (0.97)	95 (1.33)	-0.36 (-0.71, -0.01)
AEs Leading to Permanent Study Drug Discontinuation	65 (0.91)	63 (0.88)	0.03 (-0.28, 0.34)
AEs with Outcome of Death	3 (0.04)	2 (0.03)	0.01 (-0.05, 0.08
Drug Related AEs	151 (2.12)	376 (5.28)	-3.15 (-3.77, -2.54)
J-Rocket Study			
AEs	105 (16.4)	95 (14.9)	1.56 (-2.42, 5.55
SAEs	7 (1.10)	1 (0.16)	0.94 (0.08, 1.80
AEs Leading to Permanent Study Drug Discontinuation	5 (0.78)	4 (0.63)	0.16 (-0.76, 1.07)
Drug Related AEs	18 (2.82)	28 (4.38)	-1.56 (-3.61, 0.48)

Percentages calculated with the number of subjects in each group as denominator.
Based on MedDRA version 12.1; Incidence is based on number of subjects, not number of events.
Hepatic disorder AEs as identified by the Standardized MedDRA Query (SMQ)
Post-baseline: events that start on or after the first dose of study drug.
Treatment-Emergent: events that start on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Hepatic Disorder AE with outcome of death: Subject is only included once but may have had more than one adverse event with an outcome of death.
(a): Estimate and 95% confidence interval for the difference in incidence proportion between the Rivaroxaban and warfarin treatment groups (Rivaroxaban - warfarin) will be based on asymptotic methods for a single 2x2 table. The confidence interval will be calculated if there are at least 5 events (both treatment groups combined) and at least 1 event in each treatment group.

AEs with Outcome of Death

In the ROCKET Study, there were 5 hepatic disorder adverse events with a fatal outcome (rivaroxaban 3, warfarin 2). In the 3 rivaroxaban subjects, the AEs were hepatic neoplasm malignant in 2 subjects and hepatic cancer metastatic in one subject. In all 3 cases, the adjudicated causes of death was assessed as malignancy and the investigator considered the event not related to study drug. For the warfarin subjects, the AEs were hepatic cancer metastatic in one subject and acute hepatic failure in another subject. The adjudicated causes of death were malignancy and CHF/cardiogenic shock, respectively. The investigators considered the events not related to study drug. Of these 5 subjects, 2 cases were sent to HEAC for assessment. For

both cases, 2 reviewers considered the death related to the liver event and all 3 reviewers considered the relationship to study drug to be excluded.

In the J-ROCKET study, no hepatic events with a fatal outcome were reported in either treatment group.

SAEs

In the ROCKET study, the majority of SAEs were laboratory abnormities that occurred in 0.60% (43/7111) of the subjects in the rivaroxaban treatment group compared with 0.81% (58/7125) subjects in the warfarin treatment group. These reported laboratory adverse events most frequently included increases of INR (0.23% with rivaroxaban and 0.29% with warfarin), the reported terms LFT abnormal (0.14% with rivaroxaban and 0.20% with warfarin), hepatic enzyme increased (0.11% with rivaroxaban and 0.18% with warfarin), and ALT increased (0.10% with rivaroxaban and 0.03% with warfarin).

In the J-ROCKET study, 7 SAEs in the rivaroxaban group were 3 (0.47%) of increased INR that occurred more than 2 days after the stop of study drug, 2 of LFT abnormal, and 1 each of liver disorder and liver abscess. The warfarin subject had a SAE of LFT abnormal. Six SAEs resolved and 2 SAE improved.

AEs leading to Permanent Study Drug Discontinuation

In the ROCKET study, the incidence of hepatic disorder adverse events resulting in permanent discontinuation of study drug was 0.91% (65/7111) subjects in the rivaroxaban group and 0.88% (63/7125) subjects in the warfarin treatment group. The majority of these events were laboratory abnormalities and included LFT abnormal, ALT increased, and hepatic enzyme increased.

In the J-ROCKET study, 3 (0.47%) rivaroxaban subjects and 2 (0.31%) warfarin subjects discontinued study drug for the event of hepatic function abnormal. For the remaining 2 rivaroxaban subjects, 1 subject each discontinued for cholestasis and ALT increased whereas the remaining 2 warfarin subjects permanently discontinued study drug for INR increased (1 subject) and LFT abnormal (1 subject).

Common AEs

In ROCKET study, the majority of post-baseline hepatic disorder adverse events were laboratory abnormalities, which occurred in 4.5% (320/7111) of the subjects in the rivaroxaban treatment group compared with 7.9% (563/7125) of subjects in the warfarin treatment group. These reported laboratory adverse events most frequently included increases of ALT, AST, bilirubin, and hepatic enzyme, the reported term liver function test abnormal and INR increased (see Table below). All other adverse events were comparable between the groups with the exception of a possible increase in ALT increased (2.1% in the rivaroxaban group compared with 1.6% in the

warfarin group). As expected, hepatic adverse events related to INR increases were less frequent in the rivaroxaban group compared with the warfarin group (0.89% vs. 4.62%).

	Rivaroxaban	**Warfarin**
Preferred term	(N=7111)	(N=7125)
	n (%)	n (%)
Alanine aminotransferase increased	147 (2.07)	114 (1.60)
International normalised ratio increased	63 (0.89)	329 (4.62)
Liver function test abnormal	45 (0.63)	29 (0.41)
Blood bilirubin increased	44 (0.62)	57 (0.80)
Hepatic enzyme increased	26 (0.37)	32 (0.45)
Aspartate aminotransferase increased	28 (0.39)	27 (0.38)
Hepatic steatosis	22 (0.31)	25 (0.35)
Hyperbilirubinaemia	16 (0.23)	12 (0.17)
Blood alkaline phosphatase increased	11 (0.15)	8 (0.11)
Hepatic cyst	10 (0.14)	8 (0.11)
Hepatic function abnormal	10 (0.14)	8 (0.11)

In the ROCKET study, post-baseline jaundice based on grouping of preferred terms (PTs) was reported in 67 (0.94%) rivaroxaban subjects and 76 (1.07%) warfarin subjects. Five (0.07%) rivaroxaban and 7 (0.10%) warfarin events were considered serious events. Permanent study drug discontinuation for such events occurred for 6 (0.08%) rivaroxaban and 5 (0.07%) warfarin subjects. Post-baseline hepatocellular liver injury based on grouping of PTs occurred in 218 (3.07%) rivaroxaban subjects and 186 (2.61%) warfarin subjects with the difference almost entirely accounted for by the individual PT of ALT increased. Serious events occurred in 25 (0.35%) rivaroxaban subjects and 33 (0.46%) warfarin subjects. AEs leading to permanent study drug discontinuation were about 0.1% higher in rivaroxaban (43 [0.60%]) than in warfarin (35[0.49%]) subjects.

In the J-ROCKET study, the majority of postbaseline hepatic disorder adverse events were laboratory abnormalities, which occurred in 10.49% (67/639) of the subjects in the rivaroxaban treatment group compared with 10.02% (64/639) of subjects in the warfarin treatment group. These reported laboratory adverse events most frequently included increases of ALT, AST, GGT, alkaline phosphatase, hepatic enzyme, and INR. Treatment emergent hepatic disorder events related to INR increases were less frequent in the rivaroxaban group compared with the warfarin group (none vs. 2.35%) and more frequent for events starting more than 2 days from stop of study drug (4.23% vs 0.31%, respectively). All other adverse events, including alanine aminotransferase increases, were generally balanced between treatment groups although hepatic steatosis events appeared to be higher with rivaroxaban and AST increased events lower.

Hepatic disorder adverse events excluding the subsearch SMQ Liver related coagulation and bleeding disturbances for the pooled ROCKET and J-ROCKET studies are shown in Table below. The incidence for all categories of adverse events was comparable between the treatment groups.

Post-baseline Hepatic Disorder Adverse Events excluding Liver Related coagulation and bleeding disturbances
In Pooled ROCKET and J-ROCKET studies

Hepatic Disorder	Rivaroxaban (N=7750)	Warfarin (N=7764)	Rivaroxaban Minus Warfarin Diff (%) 95% CI(%) (a)
Rocket Study			
AEs	361 (5.08)	338 (4.74)	0.33 (-0.38, 1.04)
SAEs	53 (0.75)	71 (1.00)	-0.25 (-0.56, 0.05)
AEs Leading to Permanent Study Drug Discontinuation	65 (0.91)	56 (0.79)	0.13 (-0.17, 0.43)
AEs with Outcome of Death	3 (0.04)	2 (0.03)	0.01 (-0.05, 0.08)
Drug Related AEs	123 (1.73)	112 (1.57)	0.16 (-0.26, 0.58)
J-Rocket Study			
AEs	82 (12.8)	79 (12.4)	0.47 (-3.17, 4.11)
SAEs	4 (0.63)	1 (0.16)	0.47 (-0.21, 1.15)
AEs Leading to Permanent Study Drug Discontinuation	5 (0.78)	3 (0.47)	0.31 (-0.55, 1.18)
Drug Related AEs	18 (2.82)	15 (2.35)	0.47 (-1.27, 2.21)
Pooled Rocket and J-Rocket studies			
AEs	443 (5.72)	417 (5.37)	0.35 (-0.37, 1.07)
SAEs	57 (0.74)	72 (0.93)	-0.19 (-0.48, 0.09)
AEs Leading to Permanent Study Drug Discontinuation	70 (0.90)	59 (0.76)	0.14 (-0.14, 0.43)
AEs with Outcome of Death	3 (0.04)	2 (0.03)	0.01 (-0.04, 0.07)
Drug Related AEs	141 (1.82)	127 (1.64)	0.18 (-0.23, 0.59)

Based on MedDRA version 13.0; Incidence is based on number of subjects, not number of events.
Hepatic disorder AEs as identified by the Standardized MedDRA Query (SMQ), excluding all terms in the sub-search SMQ: Liver related coagulation and bleeding disturbances (Level2).
Postbaseline: events that start on or after the first dose of study drug.
Treatment-Emergent: events that start on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Hepatic Disorder AE with outcome of death: Subject is only included once but may have had more than one adverse event with an outcome of death.
(a): Estimate and 95% confidence interval for the difference in incidence proportion between the Rivaroxaban and warfarin treatment groups
(Rivaroxaban - warfarin) will be based on asymptotic methods for a single 2x2 table. The confidence interval will be calculated if there are at least 5 events (both treatment groups combined) and at least 1 event in each treatment group.

VTE Treatment Trials

The reported hepatic disorder adverse events based on hepatic disorder Standardized MedDRA Query (SMQ) were lower in the rivaroxaban group in EINSTEIN DVT and PE trials as compared to comparator but slightly higher in EINSTEIN extension study in the rivaroxaban group as compared to the placebo in VTE treatment study (see table below).

Postbaseline Hepatic Disorder Adverse Events Based on Hepatic Disorder Standardized MedDRA Query (SMQ) in VTE Treatment Studies in EINSTEIN DVT, PE and EXTENSION

Hepatic Disorder	Rivaroxaban n/N (%)	Comparator n/N (%)	Riva Minus Comp Diff (%) [95% CI(%)]
EINSTEIN DVT Study			
AEs	80/1718 (4.66)	161/1711 (9.41)	-4.75 (-6.46,-3.05)
SAEs	13/1718 (0.76)	24/1711 (1.40)	-0.65 (-1.34, 0.05)
AEs Leading to Permanent Study Drug Discontinuation	7/1718 (0.41)	6/1711 (0.35)	0.06 (-0.35, 0.47)
AEs with Outcome of Death	2/1718 (0.12)	3/1711 (0.18)	-0.06 (-0.31, 0.20)
Drug Related AEs	25/1718 (1.46)	67/1711 (3.92)	-2.46 (-3.54,-1.38)
EINSTEIN Extension			
AEs	15/598 (2.51)	11/590 (1.86)	0.64 (-1.02, 2.31)
SAEs	4/598 (0.67)	1/590 (0.17)	0.50 (-0.23, 1.23)
AEs Leading to Permanent Study Drug Discontinuation	3/598 (0.50)	1/590 (0.17)	
Drug Related AEs	8/598 (1.34)	4/590 (0.68)	0.66 (-0.47, 1.79)
EINSTEIN PE Study			
AEs	100/2011 (4.97)	162/1992 (8.13)	-3.16 (-4.69,-1.63)
SAEs	13/2011 (0.65)	26/1992 (1.31)	-0.66 (-1.27,-0.05)
AEs Leading to Permanent Study Drug Discontinuation	8/2011 (0.40)	8/1992 (0.40)	-0.00 (-0.39, 0.39)
AEs with Outcome of Death	1/2011 (0.05)	0/1992 (0.00)	
Drug Related AEs	40/2011 (1.99)	83/1992 (4.17)	-2.18 (-3.25,-1.11)

The similar results seen after excluding the subsearch SMQ Liver related coagulation and bleeding disturbances in those studies (see Table below).

Post-baseline Hepatic Disorder Adverse Events Based on Hepatic Disorder Standardized MedDRA Query (SMQ) excluding the sub-search SMQ Liver Related coagulation and bleeding disturbances (Level 2)
in EINSTEIN DVT, PE and EXTENSION

Hepatic Disorder	Rivaroxaban n/N (%)	Comparator n/N (%)	Rivaroxaban Minus Comparator Diff (%) [95% CI(%)]
EINSTEIN DVT Study			
AEs	77/1718 (4.48)	123/1711 (7.19)	-2.71 (-4.27,-1.14)
SAEs	13/1718 (0.76)	19/1711 (1.11)	-0.35 (-1.00, 0.29)
AEs Leading to Permanent Study Drug Discontinuation	7/1718 (0.41)	4/1711 (0.23)	0.17 (-0.20, 0.55)
AEs with Outcome of Death	2/1718 (0.12)	3/1711 (0.18)	-0.06 (-0.31, 0.20)
Drug Related AEs	24/1718 (1.40)	36/1711 (2.10)	-0.71 (-1.58, 0.17)

EINSTEIN Extension			
AEs	14/598 (2.34)	11/590 (1.86)	0.48 (-1.15, 2.11)
SAEs	4/598 (0.67)	1/590 (0.17)	0.50 (0.23, 1.23)
AEs Leading to Permanent Study Drug Discontinuation	3/598 (0.50)	1/590 (0.17)	
Drug Related AEs	7/598 (1.17)	4/590 (0.68)	0.49 (-0.59, 1.58)
EINSTEIN PE Study			
AEs	95/2011 (4.72)	129/1992 (6.48)	-1.75 (-3.18,-0.33)
SAEs	12/2011 (0.60)	21/1992 (1.05)	-0.46 (-1.02, 0.10)
AEs Leading to Permanent Study Drug Discontinuation	6/2011 (0.30)	6/1992 (0.30)	-0.00 (-0.34, 0.34)
AEs with Outcome of Death	1/2011 (0.05)	0/1992 (0.00)	
Drug Related AEs			

Pooled Phase 3 Studies

Pooled analysis showed overall hepatic AEs, SAEs and drug-related AEs in the rivaroxaban group were comparable to the comparator group after excluding liver related coagulation and bleeding disturbances except that more patients had AEs leading to permanent study drug discontinuation (see Table below).

Post-baseline Hepatic Disorder Adverse Events Based on Hepatic Disorder Standardized MedDRA Query (SMQ) excluding the sub-search SMQ Liver Related coagulation and bleeding disturbances (Level 2)
in Pooled ROCKET, J-ROCKET, EINSTEIN DVT, PE and EXTENSION

Hepatic Disorder	Rivaroxaban (N=12077) n (%)	Comparator (N=12057) n (%)	Riva Minus Comp Diff (%) [95% CI (%)]
AEs	629 (5.21)	680 (5.64)	-0.43 (-1.00, 0.14)
SAEs	86 (0.71)	113 (0.94)	-0.23 (-0.45, 0.00)
AEs Leading to Permanent Study Drug Discontinuation	86 (0.71)	70 (0.58)	0.13 (-0.07, 0.33)
AEs with Outcome of Death	6 (0.05)	5 (0.04)	0.01 (-0.05, 0.06)
Drug Related AEs	209 (1.73)	217 (1.80)	-0.07 (-0.40, 0.26)

7.3.4. Causality Assessments

The causality assessment of liver-related events in long-term clinical studies was conducted by the Hepatic Event Assessment Committee (HEAC). The sponsor also has a Consultant Panel to further evaluate significant events identified by HEAC.

HEAC

HEAC Members

Three clinical reviewers conducted HEAC assessments for all cases that met HEAC case criteria. These HEAC clinical reviewers independently completed clinical evaluation form and provided a written narrative for each case.

HEAC Case Criteria

Cases from the clinical studies that met any of the 5 criteria listed below were assessed by the HEAC:

- A: Concurrent combined ALT >3x ULN with Total bilirubin >2x ULN
- B: Non-concurrent combined ALT >3x ULN with Total bilirubin >2x ULN, if the total bilirubin elevation occurred within the first 30 days after the ALT elevation
- C: ALT > 8xULN
- D: Death with ALT >3x ULN within 30 days of death
- E: Other (included cases of possible concern not meeting any of the 4 categories listed above).

Causality Assessments

The causality was assessed as follows:

- Definite: the drug was considered as the cause: clear time course, exclusion of other causes; typical pattern of drug-induced liver injury, and /or histology suggestive of drug-induced liver injury, absence of other drugs, positive rechallenge if available
- Probable: chronological criteria were suggestive; the etiological work-up reasonably excludes other classical challenging causes; the study drug appeared to be the most likely cause even if there is not specific clinical/histological data suggesting specifically the role of a drug
- Possible: some criteria were missing or there is a challenging diagnosis; e.g., another drug given within a compatible period; absence of ultrasound examination in a

cholestatic/mixed pattern liver injury; absence of viral screening in a cytolytic liver injury (HAV, HBV, HCV, etc).

- Unlikely: another cause appeared more likely or chronology very atypical.
- Excluded: another cause was definitely responsible or time-course not compatible: e.g., ALT had already significantly increased before the onset of treatment; or onset more than 8 weeks after discontinuation of the treatment; histological patterns not compatible.
- Not assessable: available data were too scant to allow a reasonable assessment: not clear chronology; not clear results for liver abnormalities; no data for the etiological assessment.

HEAC also provided information on any possible alternative etiologies, the type and severity of the liver injury, the occurrence of liver transplantation and for subjects who died if the liver event was responsible for the death.

Consultant Panel

At the same time that the HEAC process was implemented a consultant panel of 6 additional drug-induced liver injury (DILI) experts was formed to provide a forum for the sponsor to be able to discuss individual HEAC cases and gain insight into anticipated discordant HEAC assessments. This group of 6 DILI experts has met regularly in person or by telephone to review the subset of HEAC cases with at least 1 possible or higher causality assessment. These consultants were sent the same blinded case packets that the HEAC reviewers assessed and reviewed them individually initially without knowledge of the HEAC evaluations. After this initial independent review of each case the HEAC assessments were sent and the group met to discuss each case. Causality evaluations by this group using the HEAC definitions were captured on a 1 page evaluation form and also in the minutes from each meeting. These assessments were not shared with the HEAC reviewers and there was no interaction between the two groups. The primary presentation of external DILI expert evaluations is the HEAC assessments, but these supplemental consultant evaluations are also noted for some cases. Three of these consultants previously participated in the RECORD studies liver safety review.

Cases Reviewed by HEAC

The HEAC reviewed a total of 201 cases from long-term phase 3 studies that included 102 cases in the rivaroxaban group and 99 cases in the comparator group who met the HEAC case criteria. The following Table shows the number of cases in each category.

Overall Cases Reviewed by HEAC
in Rocket, J-Rocket; and Einstein DVT, PE and Extension studies

HEAC Criteria	Rivaroxaban n/N (%)	Comparators n/N (%)
All cases	102/12077(0.84)	99/12057(0.82)
HEAC Criteria A/B/C	86/12077(0.71)	85/12057(0.70)
HEAC Criteria A/B	44/12077(0.36)	45/12057(0.37)

A: ALT>3xULN and TB>2xULN on the same calendar day	41/12077(0.34)	43/12057(0.36)
B: ALT>3xULN followed by TB>2xULN within 30 days	29/12077(0.24)	29/12057(0.24)
C: ALT>8xULN	62/12077(0.51)	60/12057(0.50)
D: Death with ALT>3xULN within 30 days of death	17/12077(0.14)	23/12057(0.19)
E: Other	14/12077(0.12)	13/12057(0.11)

HEAC: Hepatic Event Assessment Committee

The following table shows the number of cases from each study. Over 70% of reviewed cases were from the ROCKET study. In the ROCKET study, the total number of cases sent for HEAC review (rivaroxaban 75, warfarin 76) and the number for each individual HEAC criterion were comparable between the two reatment groups.

Cases Reviewed by HEAC
in ROCKET, J-ROCKET; and EINSTEIN DVT, PE and Extension studies

HEAC Criteria	Tx Group	ROCKET n/N (%)	J-ROCKET n/N (%)	EINSTEIN DVT n/N (%)	EINSTEIN PE n/N (%)	EINSTEIN Ext.	Total n/N (%)
A	Riva	32/7111 (0.45)	3/639 (0.47)	2/1718 (0.12)	4/2011 (0.20)	0	41/12077(0.34)
	Comp	33/7125 (0.46)	3/639 (0.47)	5/1711 (0.29)	2/1992 (0.10)	0	43/12057(0.36)
B	Riva	21/7111 (0.30)	1/639 (0.16)	2/1718 (0.12)	5/2011 (0.25)	0	29/12077(0.24)
	Comp	22/7125 (0.31)	2/639 (0.31)	3/1711 (0.18)	2/1992 (0.10)	0	29/12057(0.24)
A/B	Riva	34/7111 (0.48)	3/639 (0.47)	2/1718 (0.12)	5/2011 (0.25)		44/12077(0.36)
	Comp	35/7125 (0.49)	3/639 (0.47)	5/1711 (0.29)	2/1992 (0.10)	0	45/12057(0.37)
C	Riva	44/7111 (0.62)	6/639 (0.94)	4/1718 (0.23)	7/2011 (0.35)	1/591 (0.2)	62/12077(0.51)
	Comp	45/7125 (0.63)	1/639 (0.16)	8/1711 (0.47)	6/1992 (0.30)	0	60/12057(0.50)
D	Riva	11/7111 (0.15)	0	3/1718 (0.17)	3/2011 (0.15)	0	17/12077(0.14)
	Comp	19/7125 (0.27)	0	3/1711 (0.18)	1/1992 (0.05)	0	23/12057(0.19)
E	Riva	12/7111 (0.17)	1/639 (0.16)	0	1/2011 (0.05)	0	14/12077(0.12)
	Comp	9/7125 (0.13)	2/639 (0.31)	2/1711(0.12)	0	0	13/12057(0.11)
Total	Riva	75/7111 (1.05)	9/639 (1.41)	8/1718 (0.47)	9/2011 (0.45)	1/591 (0.2)	102/12077(0.84)
	Comp	76/7125 (1.07)	5/639 (0.31)	12/1711 (0.70)	6/1992 (0.30)	0	99/12057(0.82)

(a): Any refers to any of the following 5 HEAC criteria:
A. ALT>3xULN and TB>2xULN on the same calendar day
B. ALT>3xULN followed by TB>2xULN within 30 days
C. ALT>8xULN
D. Death with ALT>3xULN within 30 days of death
E. Other (Based on a search of selected AE preferred terms)
Note: Comparators are warfarin, enoxaparin/VKA, or Placebo.

The majority of the reviewed cases were considered to be hepatocellular liver injury by HEAC (see Table below).

Summary of Cases Sent to Hepatic Event Assessment Committee (HEAC) Review where Hepatocellular was the most frequent Type of Liver Injury
Overall: ROCKET, J-ROCKET; and EINSTEIN DVT, PE and Extension

	Rivaroxaban	Comparators
HEAC Criteria	n/N (%)	n/N (%)
Any	73/12077(0.60)	59/12057(0.49)
HEAC Criteria A/B/C	68/12077(0.56)	53/12057(0.44)
HEAC Criteria A/B	27/12077(0.22)	22/12057(0.18)
ALT>3xULN and TB>2xULN on the same calendar day	25/12077(0.21)	20/12057(0.17)
ALT>3xULN followed by TB>2xULN within 30 days	19/12077(0.16)	14/12057(0.12)
ALT>8xULN	57/12077(0.47)	46/12057(0.38)
Death with ALT>3xULN within 30 days of death	11/12077(0.09)	12/12057(0.10)
Other	5/12077(0.04)	9/12057(0.07)

Note: HEAC case criteria
A: Concurrent combined ALT >3x ULN with Total bilirubin >2x ULN
B: Non-concurrent combined ALT >3x ULN with Total bilirubin >2x ULN, if the total bilirubin elevation occurred within the first 30 days after the ALT elevation
C: ALT > 8xULN
D: Death with ALT >3x ULN within 30 days of death
E: Other (included cases of possible concern not meeting any of the 4 categories listed above)

Death cases

There were 17 deaths with ALT>3xULN within 30 days of death in the rivaroxaban group and 23 similar cases in the comparator group in ROCKET, EINSTEIN DVT and ongoing Einstein PE Studies. No cases were considered to be definitely or probably related to study drug by any of the 3 reviewers. In the rivaroxaban group, one death was considered to be possibly related by all 3 reviewers and one death was considered to be possibly related by only one reviewer.

Deaths with ALT>3xULN within 30 days of death
In ROCKET, EINSTEIN DVT and ongoing EINSTEIN PE Studies

# Reviewers with Causality= Possible	Rivaroxaban (N=12077) n (%)	Comparators (N=12057) n (%)
Total number of Cases	17 (0.14)	23 (0.19)
All 3	1 (0.01)	0
2 or more	1 (0.01)	2 (0.02)
1 or more	2 (0.02)	6 (0.06)
0	15 (0.12)	15 (0.12)

The following are case summaries of these two cases in the rivaroxaban treatment group.

*Rivaroxaban case assessed as Possible by all 3 reviewers***:**

This case was reported from the EINSTEIN PE study and was assessed by the previous liver assessment panel for the RECORD studies and submitted in the original NDA.

Timeline of the events:

63Y/F, h/o chronic asthma, HTN, and DM
Baseline: LFTs normal
Day -10 to Day 6: Augmentin treatment
Day -1: PE by CT scan
Day 16: hospitalized again for respiratory decompensation and treated with Augmentin
Day 18: ALT 5371 U/L (149 x ULN), AST 10506 U/L (328 x ULN), T. Bili 67 (3.9 x ULN), AP 151 U/L (1.2 x ULN), Study drug and Augmentin were stopped.
Day 19: ALT 4635 U/L, AST 6005 U/L, T Bili 68
Day 20: ALT 3053 U/L, AST 2260 U/L, T Bili 78
Day 21: ALT 2405 U/L, AST 1048 U/L, T Bili 88
Day 22: ALT 1658 U/L, AST 824 U/L, T Bili 116
Day 23: ALT 909 U/L, AST 327 U/L, T Bili 83
Day 24: ALT 801 U/L, AST 266 U/L, T Bili 85
Day 25: ALT 729 U/L, AST 213 U/L, T Bili 121
Day 26: ALT 892 U/L, AST 626 U/L, T Bili 205, died of heart failure
Autopsy hemorrhagic centrolobular necrosis

Case Narrative:
This was a 63 year-old woman with a history of chronic asthma, hypertension, and diabetes. The patient was hospitalized (b) (6) due to asthma exacerbation and respiratory decompensation. The patient was diagnosed pulmonary embolism (b) (6) on CT scan and was randomized to the rivaroxaban group. At the time of randomization liver enzymes and bilirubin were normal. She received the study drug from 28 December 2007 to 14 January 2008 (18 days). Patient also received Augment (b) (6) during hospitalization for asthma exacerbation and respiratory decompensation. (b) (6) , the patient was discharged from hospital with clinical improvement. (b) (6) the patient was again hospitalized with a new respiratory exacerbation without clinical signs of heart failure and she started treatment with Augmentin. (b) (6) liver test showed ALT 5371 U/L (149 x ULN), AST 10506 U/L (328 x ULN), total bilirubin 64 mg/d (3.9 x ULN), alkaline phosphatase 151 U/L (1.2 x ULN). Rivaroxaban and other medication including Augmentin were stopped. Ultrasound showed acute hepatitis without biliary obstruction. Hepatitis A, B and C were excluded. (b) (6) the patient had cardiac failure with hypokinetic left ventricular and elevated cava vein pressure. (b) (6) , ALT/AST improved and total bilirubin remained increased. (b) (6) the patient died of heart failure and multi-organ failure. Autopsy was performed and showed hemorrhagic centrolobular necrosis. The case was interpreted as shock liver by one member of liver assessment panel (LAP) and toxic hepatitis by another member of LAP.

HEAC assessment:

- 1st reviewer considered possible due to compatible chronology with possible alternate etiologies identified as right-sided heart failure and Augmentin treatment.
- 2nd reviewer considered possible due to the latency duration and rapid improvement in LFTs after drug discontinuation plus consistent histopathology. Possible alternate etiology was identified as right-sided heart failure.
- 3rd reviewer considered possible due to the absence of clear documentation of shock and drug could cause this picture. Possible alternate etiology was identified as fall in BP and shock liver.

*Rivaroxaban case assessed as Possible by 1 reviewer***:**

This case was reported from the ROCKET study.

Timeline of the events:

79Y/M, h/o A. Fib, CHF, HTN, DM, peptic ulcer
Baseline: ALT/AST normal, T bili 2.1 mg/dL
(b) (6) upper GI bleeding with emergency antrectomy and duodenectomy
(b) (6) ALT 147 U/L (12 x ULN), AST 133 U/L (11 x ULN), T. bili 5.8 mg/dL (4.8 xULN), AP 148 U/L (normal)
(b) (6) died of cardiogenic shock. No autopsy
HEAC assessment: 1 possible without alternate etiology identified, 2 unlikely with alternate etiology of shock liver due to GI bleeding and hypotension

Case Narrative:

This was a 79 year-old white man with a history of atrial fibrillation, CHF, hypertension, diabetes, peptic ulcer. Social history was negative for alcohol and cigarette use. Prior medications included digoxin, omeprazole, furosemide, Eugluoon (glyburide), Aldactone and aspirin. Subject continued on aspirin therapy during the study. At the time of randomization liver transaminases were normal, but total bilirubin was above the normal range (2.1 mg/dl). He received the study drug from 29 January 2008 to 07 September 2008 (223 days), and the bilirubin levels remained slightly elevated thereafter. (b) (6) the patient was hospitalized due to upper GI bleeding. An endoscopy showed two prepyloric ulcers and emergency surgery consisting in antrectomy and duodenectomy was performed. One day (b) (6) later laboratory examination showed hepatocellular jaundice (ALT 12x ULN, total bilirubin 4.8 x ULN, AP normal). In the next day (b) (6) the patient's condition deteriorated and the patient died. No autopsy was performed. Death was attributed to cardiogenic shock. No other liver-related tests are recorded, and there is no mention of signs/symptoms of acute 1iver failure.

HEAC assessment:

- 1 reviewer considered the causality as possible based on the compatible relationship between drug intake and clinical picture, yet missing criteria do not allow excluding the role of other causes.
- 2 reviewers considered the causality as unlikely with alternate etiology identified as shock liver due to GI bleeding and hypotension.

The following table shows the possible alternate etiologies identified by HEAC in all death cases with ALT>3xULN within 30 days of death. In the both treatment groups, right-sided heart failure or hypotension was considered to be possible alternate etiology for the liver events in most of the cases.

Possible Alternate Etiology Identified by HEAC for Death Cases with ALT>3x ULN

Possible Alternate Etiologies by HEAC	Rivaroxaban (N=12077) n (%)	Comparators (N=12057) n (%)
Number of Cases	17 (0.14)	23 (0.19)
Right-sided heart failure /hypotension (shock liver)	12	15
Malignancy with liver metastases	4	1
Concomitant medications	0	4
Gallstones/gallbladder disease	0	3
Hepatitis	1	0

Cases with ALT>3 x ULN and total bilirubin >2 x ULN

The following table shows causality assessment by HEAC for concurrent and noncurrent cases with ALT>3 x ULN and total bilirubin >2 x ULN in long-term phase 3 studies. No cases were considered to be definitely related to study drug by any of 3 reviewers. Overall, 4 (0.03%) cases in the rivaroxaban group as compared to 1 (0.01%) case in the comparator group were considered to be possibly or probably related to the study drug by all 3 HEAC reviewers (see Table below). Among the 4 cases in the rivaroxaban group, 2 were from ROCKET study and 1 each was from J-ROCKET study and EINSTEIN PE study.

Seven (0.06%) cases in the rivaroxaban group and 6 (0.05%) cases in the comparator group were considered to be possibly or probably related to the study drug by at least 2 HEAC reviewers. Thirteen (0.11%) cases in the rivaroxaban group and 16 (0.13%) cases in the comparator group were considered to be possibly or probably related to the study drug by at least one HEAC reviewer. Most cases with ALT>3 x ULN and total bilirubin >2 x ULN were not considered to be related to the study drugs in both treatment groups by any of 3 HEAC reviewers.

HEAC Causality Assessment for Cases with ALT > 3 x ULN and Total Bilirubin > 2 x ULN in Long-Term Clinical Studies

# Reviewers with Causality=Probable or Possible	Rivaroxaban n/N (%)	Comparators n/N (%)
All Phase 3 Studies	**44/12077 (0.36)**	**45/12057 (0.37)**
All 3	4/12077 (0.03)	1/12057 (0.01)
2 or more	7/12077 (0.06)	6/12057 (0.05)
1 or more	13/12077 (0.11)	16/12057 (0.13)
0	31/12077 (0.26)	29/12057 (0.24)
Rocket	**34/7111 (0.48)**	**35/7125 (0.49)**
All 3	2/7111 (0.03)	1/7125 (0.01)
2 or more	4/7111 (0.06)	5/7125 (0.07)
1 or more	8/7111 (0.11)	11/7125 (0.15)
0	26/7111 (0.37)	24/7125 (0.34)
J-Rocket	**3/639 (0.47)**	**3/639 (0.47)**
All 3	1/639 (0.16)	0
2 or more	2/639 (0.31)	1/639 (0.16)
1 or more	2/639 (0.31)	2/639 (0.31)
0	1/639 (0.16)	1/639 (0.16)
Einstein DVT	**2/1718 (0.12)**	**5/1711 (0.29)**
All 3	0	0
2 or more	0	0
1 or more	1/1718 (0.06)	2/1711 (0.12)
0	1/1718 (0.06)	3/1711 (0.18)
Einstein PE	**5/2011 (0.25)**	**2/1992 (0.10)**
All 3	1/2011 (0.05)	0
2 or more	1/2011 (0.05)	0
1 or more	2/2011 (0.10)	1/1992 (0.05)
0	3/2011 (0.15)	1/1992 (0.05)

In the rivaroxaban group, among the 13 cases with ALT>3xULN and total bilirubin >2 x ULN that were considered to be possibly or probably related to the study drug by at least one HEAC reviewer, 8 were from the ROCKET study, 2 were from the J-ROCKET study, 2 were from EINSTEIN PE study and 1 was from EINSTEIN DVT study.

The following table summarizes the causality assessment with possible alternate etiologies identified by HEAC, further causality assessment by the sponsor's consultant panel, clinical symptoms and signs, and outcomes for the 8 cases in the ROCKET study. One case was considered to be probably related to the study drug by all 3 HEAC reviewers as well as by all 6 consultant panel reviewers. No alternate etiologies were identified in this patient and ALT decreased by 50% in 5 days after rivaroxaban was discontinued. The event was resolved in 2 months. Another case was considered to be possibly related to the study drug by all 3 HEAC reviewers and also by all 6 consultant panel members. No alternate etiologies were identified in this patient and the event was resolved in 7 days while rivaroxaban continued. One additional

case was considered to be possibly related without clear alternate etiologies identified and was also considered to be possibly related by 3 of 6 consultant panel members. This patient had increased ALT and total bilirubin one month after rivaroxaban was stopped due to consent withdrawal and no additional information was available. In the remaining 5 cases, the identified possible alternate etiologies were hepatitis (2 cases), CMV and concomitant use of Augmentin, gallstones/gallbladder disease, or fall in blood pressure. Among all 8 cases, the event resolved between 7 days to 2 months in 4 cases after treatment discontinued and 7 to 24 days in 2 cases while rivaroxaban was continued. One patient was lost to follow-up and one patient died. The death case has been described earlier in this review and all 3 HEAC reviewers considered the liver event to be possibly related to rivaroxaban with possible alternate etiologies of right-sided heart failure and shock liver. However, all 6 consultant panel members considered the death as unlikely related to study drug and alternate etiologies were right-sided heart failure and fall in blood pressure.

Possible or Probable Related Cases with ALT>3xULN and Total Bilirubin >2 x ULN by HEAC in ROCKET Study

Subject#	HEAC		Consultant panel causality assessment	ALT/T.Bili	Clinical symptoms and signs	Outcomes
	Causality assessment	Possible alternate etiologies				
106725 58/F/ White	Probable-3	No alternate etiologies-3	Probable-6	Day 219: ALT 8xULN T. Bili >2xULN	No	Discontinued Tx. ALT↓50% in 5 days. Resolved in 2 months
104083 87/F/ Asian	Possible-3	No alternate etiologies-3	Possible-6	Day 197: ALT 3xULN T. Bili >2xULN	No	Continued Tx. Resolved in 7 days.
103861 73/M/ White	Possible-2 Unlikely-1	CMV +Augmentin-3	Possible-6	Day 171: ALT 3xULN Day 179: T. Bili >2xULN	No	Discontinued Tx. Resolved in 25 days
103877 73/F/ White	Possible-1 Excluded-1 Not assessable-1	No alternate etiologies-3	Possible-3 Unlikely-2 Not assessable-1	Day 323: ALT 4xULN Day 346: ALT 1xULN T. Bili >2xULN AP 3XULN	Unknown	Discontinued Tx on Day 292 due to withdrawal of consent.
100792 48/M/ White	Possible-2 Excluded-1	Hepatitis B reactivation-3	Unlikely-6	Day 673: ALT 16xULN T. Bili 4x ULN	Fatigue and jaundice	Discontinued Tx. Resolved in 30 days.
105128 78/M/ Asian	Possible-1 Unlikely-1 Excluded-1	Gallstones/ gallbladder disease-2 Nonalcoholic steatohepatitis-1	Possible-1 Unlikely-5	Day 532: ALT 3xULN Day 537: T. Bili 2x ULN	No	Continued Tx. Resolved in 24 days.

105059 78/M/ White	Possible-1 Unlikely-2	No alternate etiology-1 Heart failure+ fall in blood pressure (shock liver)-1 Fall in blood pressure (shock liver)-1	Unlikely-6	Day 224: ALT 12 XULN AST 11 XULN T. Bili: 4X ULN	Day 223: Upper GI bleeding, Emergency antrectomy and duodenectomy	Day 225: Death
107703 69/F/ White	Possible-1 Unlikely-1 Excluded-1	Hepatitis B-1 Nonalcoholic steatohepatitis-1 Hepatitis B+ Nonalcoholic steatohepatitis-1	Unlikely-6	Day 751: ALT 4XULN T. Bili 2 X ULN	No	Complete Tx on Day 750. Resolved in 7 days

The following table shows the remaining 5 cases with ALT>3xULN and total bilirubin >2 x ULN in the rivaroxaban group that were considered to be possibly or probably related to the study drug by at least one HEAC reviewer in other studies. Among the 5 cases, 3 were considered to be possibly or probably related to study drug by at least 2 reviewers, and 2 of them had possible alternate etiologies identified and one had no alternate etiology identified. The event was resolved in 4 cases and no additional information available in 1case.

Possible or Probable Related Cases with ALT>3xULN and Total Bilirubin >2 x ULN by HEAC in J-ROCKET, EINSTEIN DVT, PE and EXTENSION Studies

Study	Subject#	HEAC		Consultant Panel causality assessment	ALT/T.Bili	Clinical Symptoms	Outcomes
		Causality assessment	Alternate etiologies				
J-ROCKET	200940010 65/M/ Asian	Probable-1 Possible-2	No alternate etiology-3	Possible-6	Day 75: ALT 8x ULN T. Bili 2 xULN AP 1.9 XULN	Abdominal pain and nausea	Discontinued Tx. Resolved in 10 days
	201310004 66/M/ Asian	Probable-1 Possible-1 Excluded-1	Allopurinol-1 R-heart failure-2	Probable-1 Possible-5	Day 14: ALT 7x ULN T. Bili 9 xULN AP normal	Anorexia and "queasy"	Discontinued Tx. Resolved in 2 months
Einstein DVT	390034016 53/M/ White	Probable-1 Unlikely-2	No alternate etiology-3	Possible-5 Unlikely-1	Day 178: ALT 7x ULN T. Bili 2 xULN at baseline	No	Discontinued Tx. Remained elevated. Resolved in 4 months

EINSTEIN PE	160183005 63/F	Possible-3	Augmentin/ R-Heart Failure-1 Paroxetine/\ R-heart Failure-1 Augmentin/ Fall in BP (shock liver)-1	Unlikely-6	Day 18: ALT 149 x ULN), AST 328 x ULN), T. Bili 3 x ULN AP normal	Dyspnea and asthenia	Deaths on Day 26 (heart failure)
	100053009 29/M/ White	Possible-1 Unlikely-1 Excluded-1	No alternate etiology-2 Pre-existing liver disease-1	Unlikely-6		Not provided	Not provided

The following table shows the possible etiologies identified by at least 2 HEAC reviewers for cases with ALT>3 x ULN and total bilirubin >2 x ULN in long-term studies.

Possible Etiologies Identified for Cases with ALT>3 x ULN and Total Bilirubin >2 x ULN by at least 2 HEAC Reviewers

Possible alternate etiologies	Rivaroxaban (N=12077) n (%)	Comparators (N=12057) n (%)
All Phase 3 Studies	**44**	**45**
No alternate etiologies identified	6	0
Gallstones/Gallbladder disease	14	16
R-sided HF/Hypotension (shock liver)	10	14
Hepatitis	6	5
Malignancy with liver metastases	5	2
Concomitant medications	2	2
CMV infection	1	1
Pre-existing liver disease/alcohol abuse	0	3
Nonalcoholic steatohepatitis	0	1
ROCKET	**34**	**35**
No alternate etiologies identified	3	0
Gallstones/Gallbladder disease	12	12
R-sided HF/Hypotension (shock liver)	6	12
Hepatitis	6	4
Malignancy with liver metastases	4	1
Concomitant medications	1	1
CMV infection	1	1
Pre-existing liver disease	1	2

Nonalcoholic steatohepatitis	0	1
J-ROCKET	**3**	**3**
No alternate etiologies identified	1	0
Gallstones/Gallbladder disease	1	2
Concomitant medications	1	0
R-sided HF/Hypotension (shock liver)	1	1
EINSTEIN DVT	**2**	**5**
No alternate etiologies identified	1	0
Malignancy with liver metastases	1	1
Gallstones/Gallbladder disease	0	1
CHF/Hypotension	0	1
Concomitant medications	0	1
Alcohol abuse	0	1
EINSTEIN PE	**5**	**2**
No alternate etiologies identified	1	0
CHF/Hypotension	3	0
Gallstones/Gallbladder disease	1	1
Hepatitis	0	1

Cases with ALT >8 x ULN

The following table shows the causality assessment for cases with ALT >8 x ULN by HEAC. No cases were considered to be definitely or probably related to study drug by any of 3 reviewers. Overall, 16 (0.13%) cases in the rivaroxaban group as compared to 6 (0.05%) case in the comparator group were considered to be possibly or probably related to the study drug by all 3 HEAC reviewers (see Table below). Twenty-three (0.19%) cases in the rivaroxaban group and 18 (0.15%) cases in the comparator group were considered to be possibly or probably related to the study drug by at least 2 HEAC reviewers. Thirty (0.25%) cases in the rivaroxaban group and 31 (0.26%) cases in the comparator group were considered to be possibly or probably related to the study drug by at least one HEAC reviewer. About one half of case with ALT>3 x ULN and total bilirubin >2 x ULN were not considered to be related to the study drugs in both treatment groups by any of 3 HEAC reviewers. The majority of cases were from the ROCKET study.

Causality Assessment for Cases with ALT>8xULN in Long-Term Phase 3 Studies

# Reviewers with Causality= Probable or Possible	**Rivaroxaban n/N (%)**	**Comparators n/N (%)**
Total number of cases in all phase 3 studies	**62/12077 (0.51)**	**60/12057 (0.50)**
All 3	16/12077 (0.13)	6/12057 (0.05)
2 or more	23/12077 (0.19)	18/12057 (0.15)
1 or more	30/12077 (0.25)	31/12057 (0.26)
0	32/12077 (0.26)	29/12057 (0.24)
ROCKET	**44/7111 (0.62)**	**45/7125 (0.63)**

All 3	8/7111 (0.11)	5/7125 (0.07)
2 or more	14/7111 (0.20)	12/7125 (0.17)
1 or more	19/7111 (0.27)	20/7125 (0.28)
0	25/7111 (0.35)	25/7125 (0.35)
J-ROCKET	**6/639 (0.94)**	**1/639 (0.16)**
All 3	1/639 (0.16)	0
2 or more	2/639 (0.31)	1/639 (0.16)
1 or more	4/639 (0.63)	1/639 (0.16)
0	2/639 (0.31)	0
EINSTEIN DVT	**4/1718 (0.23)**	**8/1711 (0.47)**
All 3	3/1718 (0.17)	1/1711 (0.06)
2 or more	3/1718 (0.17)	5/1711 (0.29)
1 or more	3/1718 (0.17)	7/1711 (0.41)
0	1/1718 (0.06)	1/1711 (0.06)
EINSTEIN PE	**7/2011 (0.35)**	**6/1992 (0.30)**
All 3	3/2011 (0.15)	0
2 or more	3/2011 (0.15)	0
1 or more	3/2011 (0.15)	3/1992 (0.15)
0	4/2011 (0.20)	3/1992 (0.15)
EINSTEIN Extension	**1/590 (0.17)**	**0**
All 3	1/590 (0.17)	0

In the rivaroxaban group, among the 62 cases with ALT > 8 x ULN, 25 cases had no concurrent or non-concurrent total bilirubin increase >2 xULN. The causality and outcomes of those patients are summarized in the Table below. Overall, the event resolved in 17 cases between 2 weeks and 6 months after rivaroxaban was discontinued and resolved in 5 cases in 1 month while rivaroxaban continued. In the remaining 3 cases, 2 had treatment temporary disruption and one had no information available.

The outcome of Cases with ALT > 8 x ULN only in Lon-term Studies

Study	Causality Assessment by HEAC reviewers	Number of cases	Outcomes
ROCKET	Probable by 1 or more	7	Discontinued Tx and resolved in 2 weeks-6 months
	Possible by 2	5	2 Discontinued Tx and resolved in 2 -3 months 3 Continued Tx and resolved in 1 month
	Possible by 1	4	1 Discontinued Tx and resolved in 2 weeks 2 continued Tx and 1 stopped later 1 stopped for 1 day and resolved in 40 days
J-ROCKET	Possible by 2	1	Discontinued Tx and resolved in 2 months.
	Possible by 1	2	1 Continued and resolved in 1 month 1 stopped Tx and resolved in 10 days. Tx re-started.
EINSTEIN DVT	Probable by at 1 or more	1	Discontinued Tx and resolved in 40 days
	Possible by 3	2	Discontinued Tx and resolved in 20-30 days

EINSTEIN PE	Probable by 1 or more	2	1-Discontinued Tx and improved in 20 days 1-not provided
EINSTEIN Extension	Probable by 1 or more	1	Discontinued Tx and resolved in 2 months

Cases with Other Criteria Only

Fourteen cases in the rivaroxaban group and 13 cases in the comparator group were evaluated based on other criteria by HEAC. Among the 14 cases in the rivaroxaban group, 4 cases were considered to be possibly or probably related to the study drug by at least 1 HEAC reviewer (see Table below). Of those, the event resolved within 2 months in 3 cases after rivaroxaban was discontinued and in 1 case while rivaroxaban was continued.

Causality assessment in cases with other criteria by HEAC

Studies	Subject#	HEAC		Consultant Panel Causality assessment	ALT/T.Bili	Clinical symptoms	Outcomes
		Causality assessment	Alternate etiologies identified				
ROCKET	109091 59/F/White	Possible-3	No alternate etiology-2 Rosuvastatin-1	Possible-5 Unlikely-1	Day 15: ALT 4x ULN AST 1.5 x ULN	No	Continued Resolved in 2 months
	108479 79/M/White	Possible-2 Unlikely-1	Hepatitis C-2 Nonalcoholic steatohepatitis-1	Possible-5 Unlikely-1	Day 36 (peak): ALT 6x ULN AST 9x ULN T. Bili 1.6 x ULN	No	Discontinued Resolved in 2 months
	116381 74/F/White	Possible-2 Unlikely-1	Pre-existing liver disease-1 Tramadol-2	Unlikely-4 Not assessable-2	Day 174: T. Bili 3 x ULN AP 1.8 xULN ALT/AST not done	Jaundice on Day 174	Discontinued on Day 152 due to scheduled surgery. Improved in 1 week
J-ROCKET	201180008 71/M/Asian	Possible-1 Unlikely-2	No alternate etiology-2 R-heart failure-1	Possible-2 Unlikely-4	Day 334 ALT 1.27 x ULn AST 1.25 x ULN	No	Discontinued Resolved in 2 months

The possible alternate etiologies were identified in the majority of cases in both treatment groups (see Table below).

Possible etiologies identified in cases with other criteria by HEAC

Possible alternate etiologies identified by HEAC reviewers	Rivaroxaban (N=12077) n (%)	Comparators (N=12057) n (%)
Number of Cases	**14**	**13**
ROCKET	**12**	**9**
No alternate etiologies identified by 3	0	2
No alternate etiologies by 2, identified by 1	1	0
Gallstones/Gallbladder disease	3	0
CHF/Hypotension	0	1
Hepatitis	4	2
Malignancy with liver metastases	2	1
Concomitant medications	0	2
CMV infection	0	1
Pre-existing liver disease	1	0
Nonalcoholic steatohepatitis	1	0
J-ROCKET	**1**	**2**
No alternate etiologies by 2, HF-1	1	1
Hypotension/Sepsis	0	1
EINSTEIN DVT	**0**	**1**
Pre-existing liver disease	0	1
EINSTEIN PE	**0**	**1**
Gallstones/Gallbladder disease	0	1

7.4 Ischemic Stroke in Long-term Clinical Studies

The sponsor provided a summary of occurrence of ischemic stroke based on available long-term clinical studies to address safety concerns for possible rebound events after rivaroxaban is discontinued.

The provided data are the centrally adjudicated results, except for the Phase 2 DVT treatment studies (11223 and 11528) where no adjudication of these events was done. For these two studies, a comprehensive search of adverse event terms indicating cerebral ischemia or infarction was used to identify cases (including transient ischemic attack). For the studies with central adjudication results, only confirmed ischemic strokes are reported (i.e. hemorrhagic strokes and strokes with unknown etiology are not included). For the EINSTEIN studies, adjudicated results include all ischemic strokes reported either from the adjudication of cerebrovascular events or deaths (these two assessments were done separately). Two definitions of "on treatment" events are provided ("up to the last dose plus 1 day" [1 day definition] and "up to the last dose plus 2 days" [2 day definition]) along with the corresponding "off treatment" analyses. The 1 day definition matches the analyses done for "off-treatment" events in the RECORD studies in the original NDA submission. The 2 day definition matches the primary efficacy analysis and corresponding "off-treatment" analysis in the ROCKET studies. Since the exact time of the last study drug dose or the time of stroke onset was not collected in most studies, these analyses are

based on calendar days with the 1 day definition representing a minimum of about 24 hours since last dose and a maximum of about 48 hours. Descriptive statistics are provided for each study, including number of subjects with events, number of total valid subjects and raw incidences of events in percent (%). Due to the different study designs, patient populations, comparators and exposures of the study drug across studies, comparison of incidences between studies should be avoided. As would be expected the studies with the most ischemic stroke events were those evaluating stroke prevention in atrial fibrillation patients (ROCKET and J-ROCKET) where the number of ischemic strokes was less for rivaroxaban than for the warfarin comparator for both the 1 day and 2 day definitions. For the other studies, numbers of events were generally similar and in some cases lower for rivaroxaban than for comparator in all the studies. In addition, since there were no events on Day 2, the 2 definitions showed identical results.

Incidence of Ischemic Stroke (Central Adjudication)
(On-Treatment is defined as from the First Dose up to Last Dose Plus 2 Days)

Study	On Treatment (From the first dose up to last dose plus 2 days)		Off Treatment (From day 3 to day 30 after the last dose)	
	Rivaroxaban n/N(%)	Comparators[a] n/N(%)	Rivaroxaban n/N(%)	Comparators[a] n/N(%)
ROCKET	149/7061 (2.1)	161/7082 (2.3)	46/6843 (0.7)	35/6807(0.5)
J-ROCKET	7/639 (1.1)	17/639 (2.7)	10/628 (1.6)	3/630 (0.5)
EINSTEIN DVT	3/1718 (0.2)	5/1711 (0.3)	1/1423 (<0.1)	3/1410 (0.2)
EINSTEIN EXTENSION	0/598 (0.0)	1/590 (0.2)	0/598 (0.0)	0/590 (0.0)
EINSTEIN PE	7/2011 (0.3)	5/1992 (0.3)	3/1491 (0.2)	1/1482 (<0.1)
ATLAS ACS TIMI 46	3/2309 (0.1)	4/1153 (0.3)	2/2219 (0.1)	2/1109 (0.2)
ODIXa-DVT*	0/478 (0.0)	2/126 (1.6)	1/478 (0.2)	0/126 (0.0)
EINSTEIN Phase 2 DVT*	1/405 (0.2)	0/137(0.0)	0/405 (0.0)	0/137 (0.0)

*not adjudicated events
Note: The on-treatment events were events that had an onset not later than 1 day after the last intake of study drug.
[a]: Comparators: Warfarin, Enoxaparin/VKA, (LMW) Heparin /VKA, or Placebo.
For Rocket study, the SITE=042012 was excluded.

Incidence of Ischemic Stroke (Central Adjudication)
(On-Treatment is defined as from the First Dose up to Last Dose Plus 1 Day)

Study	On Treatment (From the first dose up to last dose plus 1 day)		Off Treatment (From day 2 to day 30 after the last dose)	
	Rivaroxaban n/N(%)	Comparators[a] n/N(%)	Rivaroxaban n/N(%)	Comparators[a] n/N(%)
ROCKET	148/7061 (2.1)	157/7082 (2.2)	47/6862 (0.7)	39/6840 (0.6)
J-ROCKET	7/639 (1.1)	17/639 (2.7)	10/629 (1.6)	3/633 (0.5)
EINSTEIN DVT	3/1718 (0.2)	5/1711 (0.3)	1/1423 (<0.1)	3/1410 (0.2)
EINSTEIN EXTENSION	0/598 (0.0)	1/590 (0.2)	0/598(0.0)	0/590 (0.0)
EINSTEIN PE	7/2011 (0.3)	5/1992 (0.3)	3/1491 (0.2)	1/1482 (<0.1)
ATLAS ACS TIMI 46	3/2309 (0.1)	4/1153 (0.3)	2/2227 (0.1)	2/1111 (0.2)

ODIXa-DVT*	0/478 (0.0)	2/126 (1.6)	1/478 (0.2)	0/126 (0.0)
EINSTEIN Phase 2 DVT*	1/405 (0.2)	0/137(0.0)	0/405 (0.0)	0/137 (0.0)

*not adjudicated events
Note: The on-treatment events were events that had an onset not later than 1 day after the last intake of study drug.
[a]: Comparators: Warfarin, Enoxaparin/VKA, (LMW) Heparin /VKA, or Placebo.
For Rocket study, the SITE=042012 was excluded.

In the ROCKET and J-ROCKET studies there were more ischemic stroke events during off treatment period using both definitions in the rivaroxaban group compared with the warfarin group. The sponsor's explanations for this observation was that the transition from blinded rivaroxaban to open-label vitamin K antagonist therapy resulted in a differential exposure of rivaroxaban subjects to subtherapeutic INR levels. For the studies in VTE treatment patient populations the event rates were low and generally similar between the treatment groups.

8 Postmarket Experience

8.1 Liver safety from Post-Marketing Data

Rivaroxaban has been approved in Canada and Europe for prophylaxis of VTE in patients undergoing hip or knee replacement surgery since September 2008. The submitted post-market data included one ongoing Phase IV post-marketing surveillance study in Europe and spontaneous safety reports from Europe and Canada.

8.1.1 Phase IV Post-Marketing Surveillance Study

Study XAMOS (13802)

XAMOS is a non-randomized, non-interventional, observational cohort study. The study plans to enroll up to 15,000 subjects worldwide who are undergoing elective hip or knee arthroplasty and who receive pharmacologic treatment for the prevention of VTE at about 200 sites. The study is intended to collect data from 7,500 subjects receiving rivaroxaban 10 mg once daily and from 7,500 subjects receiving current standard care drug therapy. Patients were to be followed up until 3 months after surgery. Where possible, each site should enroll patients receiving current standard therapy in addition to patients receiving Rivaroxaban. There will be two reference exposure cohorts, one comprising all other pharmacologic agents used in VTE prophylaxis and one including all subjects treated with LMWH.

The main objectives of the study are to collect data on:

- Bleeding events reported as serious or non-serious AEs;
- Symptomatic thromboembolic events (DVT, MedDRA SMQ 'thrombotic and embolic events') reported as AEs;
- Uncommon AEs (incidence rate between 0.1% and 1%);
- All cause mortality

Extent of Exposure
As of 15 Sep 2010, 11,601 subjects undergoing hip or knee replacement surgeries have been enrolled. Of those, 5,909 subjects (50.9%) received rivaroxaban and 5,692 subjects (49.1%) received the standard of care arm. Safety data are presented for a subset of the subjects enrolled; 8,682 subjects entered into the database with at least 1 valid database entry at the date of cut-off, of which 4,488 are assigned to rivaroxaban and 4,194 are assigned to standard of care. All presented data are derived from the still ongoing and recruiting study. The presented data are not confounder-adjusted (only the final analysis will be confounder-adjusted using the propensity score methodology).

Demographics
Approximately 63% of subjects are female, 80% are white and 58% are ≥65 years of age.

Hepatic events
To date, there were no liver transplants or liver related deaths reported. Serious hepatic disorder adverse events and events leading to permanent study drug discontinuation were reported infrequently in both the rivaroxaban and standard of care groups. The incidence of hepatobiliary disorder was similar in the rivaroxaban treatment group (8, 0.2%) compared to the standard of care group (6, 0.1%). The reported hepatic events in the rivaroxaban group included hepatic function abnormal (3), cholecystitis (2), biliary colic (1), gallbladder pain (1), and hepatic steatosis (1). The reported hepatic events in the standard of care group included hypertransaminasemia (4), bile duct stone (1), and hepatic function abnormal (1). Adverse events under investigations included ALT and AST increased (0.1% for each) in the rivaroxaban group as compared to 0.3% in the standard of care group.

As this is a non-interventional study cases are reported based on adverse events and laboratory values are not collected in a systematic manner. There were no reports of combined elevations of ALT or AST >3xULN and total bilirubin >2xULN.

HEAC assessment
HEAC case criteria for postmarketing data were as follows:

- Symptomatic liver disease
- Liver disease with fatal outcome
- Concurrent ALT >3x ULN and TB>2x ULN
- ALT >8x ULN
- Other reported liver related adverse event terms (e.g., hepatic failure, hepatitis, hepatic encephalopathy)

There were 2 subjects in the rivaroxaban treatment group with liver events that were assessed by the HEAC.

Subject 160165972 was hospitalized for suspected cholecystitis. This subject met the HEAC criterion of ALT > 8x ULN (ALT value of 674 U/L) and ‘Other’. This case was assessed by the

HEAC and out of the 3 HEAC reviewers, the relationship of the study drug to the liver event was considered excluded by 2 reviewers and unlikely by 1 reviewer based on the alternative etiology of cholecystitis.

Subject 650035031 with a reported adverse event met the HEAC criterion of symptomatic liver disease (abdominal pain, distention). The subject had a history of fatty liver, and values of all liver related laboratory tests showed slight increases (ALT, alkaline phosphatase, total bilirubin).This case was assessed by the HEAC and out of the 3 HEAC reviewers, the relationship of the study drug to the liver event was considered possible by 1 reviewer and unlikely by 2 reviewers based on the alternative etiology of concomitant medication (amoxicillin-clavulanate) and fatty liver.

8.1.2 Post-marketing Spontaneous Reports

This section discusses spontaneous reports received by Bayer Global Pharmacovigilance from the approval of rivaroxaban in Canada on 15 September 2008 and in Europe on 30 September 2008 until the cutoff date of 15 September 2010.

Extent of Exposure

In Canada and Europe, rivaroxaban is to be used at a total daily dose of 10 mg (1 tablet a day) for 2 weeks in patients undergoing elective knee surgery and 5 weeks for patients undergoing elective hip surgery.

With an estimate of a treatment duration of 24.5 days/patient (50% of the patients with 35 days treatment, 50% of the patients with 14 days treatment), the cumulative exposure to rivaroxaban (XARELTO®) since 2008 (year of first launch) is estimated at 453,000 patients, excluding the clinical and observational studies (cut-off 15 September 2010).

Hepatic events

A total of 66 patients reported 122 hepatic events and included 57 patients reporting 88 serious hepatic events. The majority (84) of the 122 hepatic events were reported from the SOC Investigations. The most frequently reported events were the transaminases increased (18 cases), followed by LFT abnormal (17 cases) and GGT increased (13 cases). The most frequently reported events in the SOC Hepatobiliary Disorders were the jaundice (12 cases), followed by cholestasis (5 cases), and cytolytic hepatitis (4 cases).

Hepatic Events in Spontaneous Reports

System Organ Class (SOC) MedDRA Preferred Term	**Number of Events (%)a**
Hepatobiliary Disorders	
Jaundice	12 (18.2%)

Cholestasis	5 (7.6%)
Cytolytic hepatitis	4 (6.1%)
Cholestatic liver injury	2 (3.0%)
Hepatic function abnormal	2 (3.0%)
Hepatitis cholestatic	2 (3.0%)
Liver disorder	2 (3.0%)
Mixed liver injury	2 (3.0%)
Ascites	1 (1.5%)
Granulomatous liver disease	1 (1.5%)
Hepatitis toxic	1 (1.5%)
Ischaemic hepatitis	1 (1.5%)
Ocular icterus	1 (1.5%)
Portal hypertension	1 (1.5%)
Yellow skin	1 (1.5%)
Investigations	
Transaminases increased	18 (27.3%)
Liver function test abnormal	17 (25.8%)
Gamma-glutamyltransferase increased	13 (19.7%)
Hepatic enzyme increased	10 (15.2%)
Aspartate aminotransferase increased	6 (9.1%)
Blood bilirubin increased	6 (9.1%)
Alanine aminotransferase increased	5 (7.6%)
Blood alkaline phosphatase increased	5 (7.6%)
Hepatic enzyme abnormal	2 (3.0%)
Bilirubin conjugated increased	1 (1.5%)
Gamma-glutamyltransferase abnormal	1 (1.5%)

[a] Based on 66 cases.

In most cases, the patients were between the age of 60 and 69 years and mean and median age was 67 years. The majority of cases were females. Among those cases, most frequently, rivaroxaban was used for VTE prophylaxis after knee replacement surgery, followed by VTE prophylaxis after hip replacement surgery (see Table below).

Table 8.2-2: Distribution of Age and Sex by Indication in Spontaneous Rivaroxaban Cases Reporting Hepatic Events Through 15 September 2010

Category	VTE Prevention Hip Replacement Surgery	Knee Replacement Surgery	Thrombo-prophylaxis	Other[a]	Not Reported	Total
Age (years)						
50 - 59	3	4	2	0	2	11
60 - 69	10	8	3	0	0	21
70 - 79	1	9	2	2	1	15
80 - 90	2	2	0	0	0	4
NR	2	2	1	3	7	15
Total	18	25	8	5	10	66
Mean age[b] (years)	66	68	66	77	62	67
Median age[b] (years)	66	67	67	76.5	57	67
Sex						
Male	6	6	1	1	2	16
Female	11	19	6	1	4	41
Unknown	1	0	1	3	4	9
Total	18	25	8	5	10	66

Key: NR=not reported; VTE=venous thromboembolism
[a]: Other indications: Knee surgery (2), surgery (1), total endoprosthesis (1), VTE prevention in hip and knee replacement surgery (1).
[b]: Based on cases with reported age: hip replacement surgery, 16 cases; knee replacement surgery, 23; thromboprophylaxis, 7; other, 2; indication not reported, 3; total, 51.

The majority (54) of cases were reported from a country in the European Union.

Table 8.2-3: Region and Country of Origin for Spontaneous Rivaroxaban Cases Reporting Hepatic Events Through 15 September 2010

Region Country of Origin	Number of Cases
North America	
Canada	1
European Union	
Austria	2
Denmark	1
France	23
Germany	17
Great Britain	7
Greece	1
Ireland	3
Rest of World	
Australia	1
Indonesia	1
Mexico	1
Switzerland	8
Total	66

The time between the first rivaroxaban dose and event onset was ≤ 1 week in 26 cases, 1-2 months in 3 cases, 100 days in 1 case, and not provided in 20 cases. Rivaroxaban was discontinued in 48 cases, continued in 1 case, and not provided in 17 cases. The event was resolved in 27 cases (including the case in which rivaroxaban was continued), resolving in 18 cases, not resolved at the time of the report in 3 cases, and not provided 18 cases. One case (201018977GPV) had a fatal outcome, however the outcome of the hepatic events was reported as resolving and the death was not attributed to any hepatic event. This case described a 76-year-old male patient who developed granulomatous liver disease in the context of pulmonary sarcoidosis 7 weeks after the last dose of rivaroxaban. Death was attributed to sepsis, acute respiratory distress syndrome (ARDS), and multiorgan failure.

Of the 66 cases with hepatic adverse events, 21 cases met the HEAC case criteria for the causality assessment. Postmarketing cases were only sent to the HEAC when at least minimal information on suspect drug(s) and at least 1 relevant laboratory value was available. In addition to the 21 cases, the HEAC also assessed one additional case (201031708GPV), which had not been fully processed in the sponsor's Global Pharmacovigilance Database by the cutoff date of this report and was therefore not included in the dataset of 66 cases.

The 22 cases with information on hepatic PTs and the assessments by the 3 HEAC clinical reviewers are listed in the Table below.

Table 8.2-4: Rivaroxaban Cases Received Through 15 September 2010 and Reviewed by the Hepatic Event Assessment Committee

Case Report Number	Relevant Adverse Events (MedDRA Preferred Terms)	HEAC Assessments (Number of Reviewers)
200912422BNE	Jaundice, Blood lactate dehydrogenase increased, Blood bilirubin increased	Not assessable (3)
200914630NA	Hepatitis A, Jaundice, Liver function test abnormal, Ischaemic hepatitis	Possible (1), unlikely (2)
200917728GPV	Hepatitis cholestatic, Jaundice , Liver function test abnormal	Probable (2), possible (1)
200919841GPV	Hepatic enzyme increased	Probable (1), possible (2)
200919889GPV	Transaminases increased	Possible (2), unlikely (1)
200920705LA	Hepatic function abnormal	Possible (1), not assessable (1), excluded (1)
200934439GPV	Cytolytic hepatitis	Unlikely (2), excluded (1)
200943105GPV	Cholestatic liver injury, Liver function test abnormal	Possible (3)
201014405GPV	Gamma-glutamyltransferase increased, Transaminases increased	Possible (1), unlikely (1), excluded (1)
201018977GPV	Portal hypertension, Jaundice, Ascites, Granulomatous liver disease	Unlikely (2), excluded (1)
201026299GPV	Transaminases increased	Possible (1), unlikely (2)
201026358GPV	Hepatic enzyme increased, Jaundice	Possible (3)
201026766GPV	Jaundice, Hepatic enzyme increased	Possible (1), unlikely (2)
201030643GPV	Hepatitis cholestatic, Cytolytic hepatitis, Jaundice, Hepatic enzyme increased, Blood bilirubin increased	Possible (1), excluded (2)
201031518GPV	Hepatitis toxic, Liver function test abnormal, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Blood bilirubin increased, Ocular icterus	Probable (1), possible (2)
201033805GPV	Transaminases increased, Jaundice	Unlikely (1), excluded (2)
201034398GPV	Jaundice, Cholestasis, Hepatic enzyme increased	Possible (3)
201035043GPV	Mixed liver injury, Cytolytic hepatitis, Cholestasis	Possible (3)
201035181GPV	Mixed liver injury	Possible (1), unlikely (2)
201035209GPV	Transaminases increased	Possible (3)
201035976GPV	Cholestatic liver injury, Jaundice, Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood bilirubin increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased	Possible (3)
201031708GPV[a]	Cytolytic hepatitis	Possible (1), unlikely (1), excluded (1)

Key: HEAC=Hepatic Event Assessment Committee

a: This case had not been fully processed in the Bayer Global Pharmacovigilance Database by the cutoff date for this report and was not part of the dataset of cases retrieved with the search.

Among the 22 cases evaluated by HEAC, 9 cases were considered to be possibly or probably related to rivaroxaban treatment by all 3 reviewers, 1 additional case was considered to be possibly or probably related by 2 reviewers, other 8 cases were considered to be possibly or probably related by 1 reviewer. Three cases were considered to be unlikely related or excluded by all 3 reviewers and 1 was not assessable. The following table lists cases that were considered

to be possible or probably related to rivaroxaban by at least 2 HEAC reviewers. The sponsor's consultant panel also has assessed the 6 of 11 cases so far and also considered that the reported hepatic events in those cases were possibly or probably related to the rivaroxaban treatment by almost all members.

Possible or Probable Related Cases by at least 2 HEAC Reviewer from Post-marketing Reports

Case Report Number	Relevant Adverse Events (MedDRA Preferred Terms)	HEAC Assessments (3 reviewers)	Consultant panel (6 members)
200917728GPV	Hepatitis cholestatic, Jaundice , Liver function test abnormal	Probable-2 possible-1	Probable-1 Possible-5
200919841GPV	Hepatic enzyme increased	Probable-1 possible-2	Probable-1 Possible-5
201031518GPV	Hepatitis toxic, Liver function test abnormal, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Blood bilirubin increased, Ocular icterus	Probable-1 possible-2	Probable-1 possible-5
200943105GPV	Cholestatic liver injury, Liver function test abnormal	Possible-3	Possible-6
201026358GPV	Hepatic enzyme increased, Jaundice	Possible-3	Possible-6
201034398GPV	Jaundice, Cholestasis, Hepatic enzyme increased	Possible-3	Not available
201035043GPV	Mixed liver injury, Cytolytic hepatitis, Cholestasis	Possible-3	Not available
201035209GPV	Transaminases increased	Possible-3	Not available
201035976GPV	Cholestatic liver injury, Jaundice, Aspartate aminotransferase increased, Alanine	Possible-3	Not available
201035976GPV	Cholestatic liver injury, Jaundice, Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood bilirubin increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased	Possible-3	Not available
200919889GPV	Transaminases increased	Possible-2 unlikely-1	Possible-5 unlikely-1

Three cases are assessed as probably related by at least 1 HEAC reviewer and also by 1 consultant panel member. These include one case with concurrent ALT>3x ULN and total bilirubin >2x ULN, 1 case with ALT > 8x ULN, and 1 case with symptomatic liver disease and elevated ALT and total bilirubin. A brief summary of each case is provided below.

Probable Related Case by at least 1 HEAC Reviewer from Post-marketing Reports

Case# Relevant Adverse Events	HEAC Assessments	Consultant panel	Outcome
200917728GPV 67/F post knee surgery (b) (6) Jaundice, loss of appetite, nausea, loss of weight ALT 28xULN, AST 28xULN T. Bili 15xULN	Probable (2), possible (1) No alternate etiologies-2 Glucophage and lisinopril-1 Hepatitis A, B, C: negative Hepatitis E: not done Positive ANA	Prabable-1 Possible-5	Resolved in 2 months Tx with Legalon

Hepatitis cholestatic, Jaundice , Liver function test abnormal	Ultrasound: negative		
200919841GPV 67/F post knee surgery (b) (6) ALT 37xULN, AST 23xULN No bili data Hepatic enzyme increased	Probable (1), possible (2) No alternate etiologies-1 Acitretin-2 (on 2 years) Hepatitis A, B, C: negative Hepatitis E: not done Ultrasound: not done	Prabable-1 Possible-5	Improved in 1 month and lost to follow-up
201031518GPV 51/F, post hip surgery (b) (6) ALT 1022, AST 739 Bili 3.3, GGT 631 Hepatitis toxic, Liver function test abnormal, AST increased, ALT increased, GGT increased, Blood bilirubin increased, Ocular icterus	Probable (1), possible (2) No alternate etiologies-2 Etoricoxib-1 Hepatitis A, B, C: negative Hepatitis E: not done Ultrasound: 2 small stones	Probable-1, possible-5	Improved in 40 days

Subject 200917728GPV presented with jaundice, loss of appetite, nausea and loss of weight 41 days after starting rivaroxaban treatment and met the HEAC criterion of combined ALT with total bilirubin elevation. Two HEAC reviewers considered the event probably related to rivaroxaban with no alternative etiology identified and one reviewer considered it possible related with Metformin and lisinopril identified as possible alternative etiologies. The consultant panel further evaluated this case and all 6 reviewers considered the event probably (5) or possible (1) related to the rivaroxaban treatment. The event was resolved in 2 months with supportive treatment.

Subject 200919841GPV had ALT>8x ULN with onset (b) (6) without bilirubin data available. One HEAC reviewer considered it probable related and 2 reviewers considered the event possibly related to rivaroxaban with concomitant use of acitretin as possible alternative etiology. The consultant panel evaluated this case and all 6 reviewers considered the event probably (1) or possibly (5) related to the rivaroxaban treatment. The event improved in 1 month and the patient was lost to follow-up.

Subject 201031518GPV had symptomatic liver disease (ocular icterus) with onset (b) (6). One HEAC reviewer considered it probable related and 2 reviewers considered the event possibly related to rivaroxaban with concomitant use of etoricoxib or metamizole as possible alternative etiology. Consultant panel evaluated this case and all 6 reviewers considered the event probably (1) or possibly (5) related to the rivaroxaban treatment. The event improved in 40 days.

8.2 Other Safety Update

8.2.1 Phase IV Post-marketing surveillance

Study XAMOS (13802)

Adverse Events

Adverse events were reported in 1409 (31.4%) and 1313 (31.4%) of patients in the rivaroxaban and standard care groups, respectively. The following table summarizes AEs that have occurred in ≥2% of subjects in either treatment group. The frequency of AEs is similar in the rivaroxaban and standard of care groups. Out of these, the most frequently reported AEs that have occurred more often (at least 0.5% difference) in the rivaroxaban group compared with the standard of care group are vomiting and anemia postoperative. The most frequently reported AE that has occurred more often (at least 0.5% difference) in the standard of care group compared with the rivaroxaban group is nausea.

Table 6-2: Incidence of AEs, by SOC and Preferred Term (MedDRA Version 13.0), Occurring in ≥2% Subjects in Either Treatment Group
Subjects With any Type of Intervention in Xamos

System Organ Class MedDRA Preferred Term	Rivaroxaban 10 mg o.d. N=4488	Standard of Care N = 4194
Subjects with any adverse events	1409 (31.4%)	1318 (31.4%)
Blood and lymphatic system disorders	129 (2.9%)	143 (3.4%)
Anemia	118 (2.6%)	127 (3.0%)
Gastrointestinal disorders	325 (7.2%)	290 (6.9%)
Nausea	165 (3.7%)	182 (4.3%)
Vomiting	115 (2.6%)	88 (2.1%)
General disorders and administration site conditions	192 (4.3%)	205 (4.9%)
Pyrexia	94 (2.1%)	99 (2.4%)
Infections and Infestations	144 (3.2%)	145 (3.5%)
Injury, poisoning and procedural complications	327 (7.3%)	318 (7.6%)
Anemia postoperative	126 (2.8%)	98 (2.3%)
Investigations	268 (6.0%)	270 (6.4%)
Hemoglobin decreased	198 (4.4%)	195 (4.6%)
Nervous system disorders	88 (2.0%)	81 (1.9%)
Skin and subcutaneous tissue disorders	88 (2.0%)	67 (1.6%)
Vascular disorders	138 (3.1%)	142 (3.4%)
Uncoded	225 (5.0%)	180 (4.3%)

Note: Incidences are based on number of subjects, not number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Note: Uncoded stands for not yet coded at the time the analysis was performed

Deaths

As of 15 Sep 2010, 12 deaths were reported including 7 deaths in the rivaroxaban group and 5 deaths in the standard care group.

Among the 7 deaths in the rivaroxaban group, 3 subjects died of lung tumors and deaths occurred between 42 days and 183 days after drug administration and the investigators judged that there was no relationship to rivaroxaban treatment. One subject (male, age unknown, Netherlands) died due to an occluded coronary stent 12 days after start of rivaroxaban treatment; the death was assessed as related to rivaroxaban. Among the 3 remaining subjects, one (68-year-old female, Greece) died due to heart arrest 5 days after start of rivaroxaban treatment, 1 (63-year-old female, China) died due to chest tightness, shortness of breath, and difficulty breathing 15 days after start of rivaroxaban, and one (77-year-old male, Venezuela) died due to stroke (type unspecified) 6 days after start of rivaroxaban treatment. In all 3 cases, the death was assessed as not related to rivaroxaban.

There were 5 deaths in the standard of care group and cause of deaths included cerebral infarction with secondary bleeding, cardiac ischemia/cardiac arrest or shock in 3 cases and unknown in 2 cases. In all cases, the death was assessed as not related to standard of care.

Serious Adverse Events

SAEs were reported in 269 (6%) and 267 (6%) of patients in the rivaroxaban and standard care groups, respectively. The following table summarizes SAEs that have occurred in ≥0.2% of subjects in either treatment group. The most frequently reported SAEs that have occurred more often (at least 5 subject difference) in the rivaroxaban group compared with the standard of care group are hemoglobin decreased, pulmonary embolism, and atrial fibrillation. The most frequently reported SAEs that have occurred more often (at least 5 subject difference) in the standard of care group compared with the rivaroxaban group are anemia, pneumonia, and DVT.

Table 6-3: Incidence of SAEs, by SOC and Preferred term (MedDRA version 13.0), Occurring in ≥0.2% Subjects in Either Treatment Group
Subjects With any Type of Intervention in Xamos

System Organ Class MedDRA Preferred Term	Rivaroxaban 10 mg o.d. N=4488	Standard of Care N = 4194
Subjects with any serious adverse events	269 (6.0%)	267 (6.4%)
Blood and lymphatic system disorders	10 (0.2%)	22 (0.5%)
Anemia	10 (0.2%)	19 (0.5%)
Cardiac Disorders	16 (0.4%)	16 (0.4%)
Atrial fibrillation	8 (0.2%)	3 (0.1%)
Gastrointestinal disorders	13 (0.3%)	12 (0.3%)
General disorders and administration site conditions	25 (0.6%)	23 (0.5%)
Device dislocation	6 (0.1%)	7 (0.2%)
Edema peripheral	7 (0.2%)	5 (0.1%)
Pyrexia	7 (0.2%)	4 (0.1%)
Infections and Infestations	39 (0.9%)	51 (1.2%)
Pneumonia	1 (<0.1%)	8 (0.2%)
Wound infection	9 (0.2%)	7 (0.2%)
Injury, poisoning and procedural complications	46 (1.0%)	45 (1.1%)
Joint dislocation	4 (0.1%)	8 (0.2%)
Investigations	25 (0.6%)	15 (0.4%)
Hemoglobin decreased	16 (0.4%)	6 (0.1%)
Musculoskeletal and connective tissue disorders	15 (0.3%)	15 (0.4%)
Nervous system disorders	14 (0.3%)	17 (0.4%)
Respiratory, thoracic and mediastinal disorders	21 (0.5%)	8 (0.2%)
Pulmonary embolism	10 (0.2%)	2 (<0.1%)
Surgical and medical procedures	9 (0.2%)	9 (0.2%)
Vascular disorders	26 (0.6%)	31 (0.7%)
Deep vein thrombosis	6 (0.1%)	11 (0.3%)
Hematoma	9 (0.2%)	6 (0.1%)
Uncoded	47 (1.0%)	43 (1.0%)

Note: Incidences are based on number of subjects, not number of events. Although a subject may have had 2 or more clinical AEs, the subject is counted only once in a category. The same subject may appear in different categories.
Note: Uncoded stands for not yet coded at the time the analysis was performed

Bleeding-Related Adverse Events

Bleeding-related AEs have been reported in 140 (3.1%) and 115 (2.7%) in the rivaroxaban and standard care groups, respectively. The following table summarizes bleeding-related AEs occurring in ≥0.2% of subjects in either treatment group. The most frequently reported bleeding-related AEs that have occurred more often (at least 5 subject difference) in the rivaroxaban group compared with the standard of care group are hematoma and epistaxis. The most frequently reported bleeding-related AEs that have occurred more often (at least 5 subject difference) in the standard of care group compared with the rivaroxaban group are wound hemorrhage and operative hemorrhage.

Table 6-4: Incidence of Bleeding-Related AEs, by SOC and Preferred term (MedDRA version 13.0), Occurring in ≥0.2% Subjects in Either Treatment Group
Subjects With any Type of Intervention in Xamos

System Organ Class MedDRA Preferred Term	Rivaroxaban 10 mg o.d. N=4488	Standard of Care N = 4194
Subjects with any bleeding-related adverse events	140 (3.1%)	115 (2.7%)
Gastrointestinal disorders	6 (0.1%)	7 (0.2%)
Injury, poisoning and procedural complications	42 (0.9%)	51 (1.2%)
Operative hemorrhage	7 (0.2%)	14 (0.3%)
Post procedural hemorrhage	11 (0.2%)	9 (0.2%)
Wound hemorrhage	8 (0.2%)	17 (0.4%)
Respiratory, thoracic and mediastinal disorders	13 (0.3%)	7 (0.2%)
Epistaxis	12 (0.3%)	7 (0.2%)
Vascular disorders	44 (1.0%)	26 (0.6%)
Hematoma	44(1.0%)	25 (0.61%)

Note: If the initial treatment is not entered/not coded, the subjects will not be displayed.
Note: Bleeding-related AEs identified as preferred terms from the SMQ for "Hemorrhage." Laboratory terms were not excluded from this query, but have been deleted from this table to be consistent with other bleeding-related AE tables in this safety update.
N = Total number of subjects with (at least 1 AE reported) or (no AE reported and had answered question if any AE) or dead.

A total of 28 (0.6%) rivaroxaban subjects and 18 (0.4%) standard of care subjects have had bleeding-related SAEs. The distribution of bleeding-related SAEs is similar between treatment groups, and there are no preferred terms with a between-group difference of 5 or more subjects.

Cerebrovascular Disorder Adverse Events

Cerebrovascular disorders were reported in 7 (0.2%) rivaroxaban subjects and 10 (0.2%) standard of care subjects. Cerebrovascular disorders SAEs were reported in 4 (0.1%) rivaroxaban subjects and 9 (0.2%) standard of care subjects. Cerebrovascular disorders SAEs in the rivaroxaban group include 2 subjects with cerebrovascular accident, 1 subject with monoparesis and 1 subject with a transient ischemic attack. Serious cerebrovascular disorders in the standard of care group include 2 subjects each with cerebral infarctions, cerebrovascular accident, or transient ischemic attacks, and 1 subject each with cerebral ischemia, hemorrhagic cerebral infarction, or hemiparesis.

Thrombocytopenia
Thrombocytopenia was reported in 1 (<0.1%) subject in the rivaroxaban group and 9 (0.2%) subjects in the standard care group.

8.2.2 Spontaneous Reports

As of 15 September 2010, 1,542 spontaneous case reports, including consumer reports, with 2,879 AEs were identified, of which 2,041 were SAEs.

Deaths

Since rivaroxaban was approved for marketing in Canada on 15 September 2008, a total of 36 deaths have been spontaneously reported; 33 cases included AEs with fatal outcomes that occurred while being treated with rivaroxaban and 3 were patients who died after they had completed treatment with rivaroxaban.

Of the 33 patients who died while on treatment with rivaroxaban, 13 had fatal pulmonary embolisms, including 1 patient with 3 suspected causes of death (PE, MI, and CVA). Seven patients died of bleeding-related AEs, including 4 patients with cerebral hemorrhages. Other AEs with fatal outcome include heart disease, heart failure, myocardial infarction, esophagitis (with gastrointestinal hemorrhage)/sepsis, ileus, infection, multiorgan failure, renal failure/pneumonia, and suicide. For 4 patients, the cause of death was unknown.

For the 3 patients who died after completing treatment with rivaroxaban: 1 patient died of an unknown cause approximately 2 weeks after the last dose of rivaroxaban; a second patient died of progression of hypertension and right heart failure several months after the last dose of rivaroxaban; and the third patient died of acute respiratory distress syndrome (ARDS), multi-organ failure and sepsis also several months after the last dose.

Serious Adverse Events

SAEs that occurred at a frequency of at least 20 events are summarized in the table below. The highest number of SAEs was reported for the SOC vascular disorders (362), injury, poisoning and procedural complications (275) and gastrointestinal disorders (226). The most frequent SAEs were PE (136), DVT (135), hematoma (96), and wound secretion (79).

Table 6-5: Summary of Serious Adverse Events with Frequency of at Least 20 SAEs by System Organ Class and Preferred Term (Subjects Valid in Spontaneous Reporting)

System Organ Class Preferred Term	Number of Serious Adverse Events
Any Serious Adverse Event	2041
Blood and lymphatic system disorders	
Anaemia	26
Gastrointestinal disorders	
Gastrointestinal hemorrhage	42
Melena	25
Hematemesis	24
General disorders and administration site conditions	
Edema peripheral	56
Injury, poisoning and procedural complications	
Wound secretion	79
Post procedural hemorrhage	46
Post procedural hematoma	36
Investigations	
Hemoglobin decreased	49
Musculoskeletal and connective tissue disorders	
Hemarthrosis	45
Pain in extremity	38
Nervous system disorders	
Dizziness	34
Respiratory, thoracic and mediastinal disorders	
Pulmonary embolism	136
Dyspnea	30
Vascular disorders	
Deep vein thrombosis	135
Hematoma	96
Hemorrhage	40
Thrombosis	35

Note: Only Preferred Terms meeting the threshold of 20 events are listed in this table.
Note: The numbers are based on numbers of events.

Bleeding-Related Serious Adverse Events

The following table summarizes bleeding-related SAEs that occurred at a frequency of at least 5 events. A total of 669 cases with at least 1 bleeding event were identified. Among AEs by preferred term, the most frequent bleeding-related SAEs were hematoma (96), postprocedural hemorrhage (46), hemarthrosis (45), gastrointestinal hemorrhage (42), hemoglobin decreased (42), and hemorrhage (40).

Table 6-6: Summary of Bleeding-Related Serious Adverse Events with Frequency of at Least 5 SAEs, by System Organ Class and Preferred Term (MedDRA Version 13.0) (Subjects Valid in Spontaneous Reporting)

System Organ Class Preferred Term	Serious Adverse Events
Blood and lymphatic system disorders	
Anaemia	20
Hemorrhagic anaemia	15
Gastrointestinal disorders	
Gastrointestinal hemorrhage	42
Melena	25
Hematemesis	24
Rectal hemorrhage	14
Upper gastrointestinal hemorrhage	10
Hematochezia	8
Injury, poisoning and procedural complications	
Post procedural hemorrhage	46
Post procedural hematoma	36
Operative hemorrhage	16
Wound hemorrhage	15
Contusion	14
Subcutaneous hematoma	7
Incision site hemorrhage	6
Incision site hematoma	5
Investigations	
Hemoglobin decreased	42
Musculoskeletal and connective tissue disorders	
Hemarthrosis	45
Muscle hemorrhage	6
Nervous system disorders	
Cerebral hemorrhage	9
Renal and urinary disorders	
Hematuria	19
Reproductive system and breast disorders	
Menorrhagia	5
Respiratory, thoracic and mediastinal disorders	
Epistaxis	13
Hemoptysis	5
Skin and subcutaneous disorders	
Ecchymosis	6
Vascular disorders	
Hematoma	96
Hemorrhage	40

Note: Total AE includes non-bleeding AE – but the table displays bleeding events only and disregards non-bleeding events (preferred term terms)

Other Significant Adverse Events

Other significant adverse events identified in post-marketing report lists included cerebral hemorrhage, hypersensitivity reactions including anaphylactic shock, agranulocytosis, and Steven-Johnson syndrome.

Other Significant Adverse Events from Post-Marketing Spontaneous Report Listings

MedDRA Preferred Term	Total AEs	SAEs	Death	Probable/Possible related cases
Cerebral hemorrhage	9	9	3	7
Hemiparesis	3	3	0	2
Subdural hematoma	1	1	0	1
Agranulocytosis	3	3	1	2
Hypersensitivity	12	3	0	11
Anaphylactic reaction	2	2	0	1
Anaphylactic shock	2	2	0	2
Stevens-Johnson syndrome	1	1	0	1

The sponsor further submitted a summary of cases of agranulocytosis, Steven-Johnson syndrome, and spinal/epidural hematoma upon the Division's request based on all safety databases available (see Table below). There were 3 cases of agranulocytosis reported from post-marketing spontaneous reports with rivaroxaban, 2 cases of Steven-Johnson syndrome from postmarketing data (1 from XAMOS phase 4 surveillance study and 1 from spontaneous reports) with rivaroxaban, and 2 cases of epidural hematoma with rivaroxaban from spontaneous reports.

Term Study number	Unique Patient Identification Number	Treatment	Clinical Trial (CT) or Post marketing (PM)
Agranulocytosis			
12839	12839-28103-0001	Control	CT
Spontaneous use	CH-BAYER-201018977GPV	Rivaroxaban	PM
Spontaneous use	DE-BAYER-201029469GPV	Rivaroxaban	PM
Spontaneous use	CH-BAYER-201010007GPV	Rivaroxaban	PM
Stevens-Johnson Syndrome			
11630	RIVAROXAFL3001-063012-109501	Control	CT
11899	11899-37006-2008	Control	CT
XAMOS	XA0801C0-0184	Rivaroxaban	PM
Spontaneous use	DK-DKMA-20101032	Rivaroxaban	PM
Spinal Hematoma			
11630	RIVAROXAFL3001-002507-112160	Rivaroxaban	CT
11630	RIVAROXAFL3001-002507-114463	Control	CT
11357	11357-34001-7005	Control	CT
11356	11356-10010-6003	Control	CT
RIVAROXACS3001	RIVAROXACS3001-054009-312361	Blinded	CT
RIVAROXACS3001	RIVAROXACS3001-420017-310407	Blinded	CT
Spontaneous use	CH-BAYER-201022890GPV	Rivaroxaban	PM
Spontaneous use	IN-BAYER-2010-000014	Rivaroxaban	PM

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The following are the narrative summaries for these cases associated with rivaroxaban treatment:

Agranulocytosis:

MC#201018977GPV: A 76-year old male started Xarelto (b) (6) after knee replacement surgery (b) (6), patient was diagnosed with granulomatous hepatitis, sarcoidosis and autoimmune hemolytic anemia (warm type), which were considered serious due to hospitalization & life-threatening nature. The patient was hospitalized (b) (6). Liver biopsy (b) (6) showed granulomatoid hepatitis, distinct morphologic changes of liver parenchym, possibly co-reaction to inflammatory systemic disease with a drug-induced toxic reaction might be possible. Thoracical/pulmonary CT - high resolution (b) (6) showed pulmonary changes conformable with advanced stage of sarcoidosis. Bronchoscopy (b) (6) found chronic laryngitis & chronic tracheobronchitis conformable with pulmonary sarcoidosis. Transbronchial biopsy showed unspecific inflammation and BAL with mild lymphocytosis in normal CD4-/CD8 quotient and mild eosinophilia. The course of reported events was described as follows: portal hypertension, ascites, icterus, splenomegalia, in course of hospitalization pancytopenia with agranulocytosis. Prednisone was given for remedial treatment. Patient's condition improved and discharged (b) (6). Reporter considered the reported events as possibly related to Xarelto. The patient was hospitalized again (b) (6) for sepsis, ARDS & multiorgan failure with bilateral pneumonia under steroid therapy in presence of interstitial lung disease (sarcoidosis). The patient was intubated and had decompensated cardiac failure (cardiomyopathy in sarcoidosis). The patient died (b) (6) and autopsy showed significant hepatic fibrosis/cirrhosis. The Company considers granulomatous hepatitis as clinical manifestation of sarcoidosis and thus, following the assessment of sarcoidosis, as not related to

Xarelto. Autoimmune hemolytic anemia (AIHA) might occur along with sarcoidosis. However, no test results (e.g. positive COOMBS test, lab values) were reported to confirm the diagnosis of AIHA. Therefore and due to an unclear temporal relationship, the causal relation between AIHA and Xarelto is currently not assessable. Regarding agranulocytosis, which is not typical manifestation of sarcoidosis, clarification of temporal association as well as corroborating lab data is required first to perform a proper assessment of causal relation to Xarelto.

MC#201029469GPV: An 80 year-old Caucasian female started Xarelto (rivaroxaban) 10 mg daily for thrombosis prophylaxis after knee surgery (b) (6). Novalgin had been given for postoperative analgetic treatment. (b) (6), patient developed agranulocytosis with fibrin-covered aphthous stomatitis. Laboratory findings revealed a decrease of leucocytes to 3.9 G/L. Xarelto and Novalgin were withdrawn. The leucocytes dropped further to a minimum of 0.4 G/L, while hemoglobin remained unchanged on a low level and the platelets were in normal range. The event was considered serious as it required her transfer from orthopedic department to acute care (b) (6). On an unreported date, patient also experienced thrombocytosis, considered non-serious. For remedial therapy patient received Piperacillin and Tazobactam for one week, afterwards it was switched to Cefuroximaxetil. The fibrin-covered aphthous stomatitis was locally treated with Candio-Hermal and Hexoral. After the treatment, the local inflammation subsided clearly, the leucocytes returned to normal, and C-reactive protein dropped. Patient's condition recovered from agranulocytosis and thrombocytosis, and it improved from fibrin-covered aphthous stomatitis. The clinician assessed agranulocytosis and thrombocytosis to be probably related to Novalgin and the relationship between agranulocytosis and Xaralto as not assessable. Although concomitant co-suspect drug Metamizole as well as the preceding surgical intervention are a plausible explanation for the respective events, company cannot exclude an at least contributory action of suspect drug Xarelto in the development of the event due to a compatible temporal relationship. Metamizole is a well-recognized causative agent for agranulocytosis. Furthermore, thrombocytosis is considered a reactive consequence of the preceding TEP implantation.

MC#201010007GPV: A 78 year-old male (Switzerland) received Xarelto (rivaroxaban) 10 mg daily after right knee replacement (b) (6) patient experienced agranulocytosis, considered serious due to hospitalization. The patient also started Pantozol (pantoprazole) and Dafalgan (paracetamol) on the day of surgery and with Esidrex (hydrochlorothiazide) 5 days post-op. In addition, patient received concomitantly Blopress plus (hydrochorothiazide/ candersatan) and fluoxetine for about 2 years. Xarelto and all treatments that could provoke a leukopenia were stopped and therapy with antibiotics was initiated because of the appearance of an outflow of the operation wound. Agranulocytosis was medically treated and resolved after two weeks without sequelae. Lab data was provided and revealed the following time course of WBC (normal range: 4.3 - 10.8 GIGA/L) and neutrophils (normal range: 45 - 74 %):

(b) (6) WBC 4.9 GIGA/L, neutrophils 57 %
: WBC 2.1 GIGA/L
: WBC 1.9 GIGA/L, neutrophils 23.6 %
: WBC 2.3 GIGA/L, neutrophils 18.2 %
WBC 5.2 GIGA/L, neutrophils 67.8 %
WBC 4.5 GIGA/L, neutrophils 62.4 %

The reporter considered the diagnosis agranulocytosis to be possibly related to Xarelto and to be unlikely related to pantoprazole sodium. The company considered that due to a given temporal relationship a causal relation Xarelto and the occurrence of agranulocytosis cannot be excluded. The company also considered hydrochlorothiazide as an alternative explanation.

Steven-Johnson syndrome:

MC# 201019897LA: This case was report from XAMOS phase 4 surveillance study from Colombia. The patient's age and gender, relevant medical history/concurrent conditions/concomitant medications were not provided. Patient received XARELTO (rivaroxaban) at a total daily dose of 20 mg for thrombosis prophylaxis. An unspecified number of days after initiating rivaroxaban, the patient experienced an infection grade 4. Approximately 39 days after start of the infection, the patient experienced Stevens-Johnson syndrome (SJS). It was not reported if rivaroxaban therapy continued. The investigator considered the diagnoses Stevens-Johnson syndrome and infection grade 4 not to be associated, an alternative explanation was not provided. The company agreed with the investigator's causality assessment (not associated) for the reported events and considered the intercurrent infection grade 4 a plausible alternative explanation to the Stevens-Johnson syndrome. No additional information was provided.

MC# 201018606GPV: A 72 year-old male started Xarelto 10 mg daily (b) (6) after knee replacement surgery. This case was reported from the regulatory authority of Denmark. (b) (6) patient experienced general malaise, fever over 40 degrees, and skin rash and the events was reported as "anaphylactic reaction". Rash started on the operated leg spread to scrotum, trunks and the other leg as papular, erythematous, infiltrated rashes. A half day later a rash appeared in the mouth with gray-yellow plaques and edema. The patient had an intubation after approx 10 hours due to edema of the throat. The skin began to loosen and a liquid came from the denudation of the skin. The patient was transferred to the burns unit a day after admission. Knee puncture and blood culture were negative. There were leukocytes at 18.9, neutrophilia, CRP of 100 at admission. X-ray of the chest showed no infiltrates. The patient was otherwise healthy and had not on other medications. (b) (6) Xarelto was withdrawn. (b) (6) skin biopsy showed erythema multiforme/Steven Johnson Syndrome. Assessment by dermatology department was Steven Johnson syndrome possibly triggered by the thrombosis prophylaxis and it did not look like as toxic epidermal necrosis (TEN) or bullous staphylococci infection. The case was initially reported as "fatal" and the authority of Denmark later confirmed that the patient didn't die. The patient was reported as 'recovered' on 25-Mar-2010. The company considered that the gentamicin-containing bone cement might be an alternative explanation for the event as the skin reaction mainly occurred in the operated leg.

Epidural hematoma:

MC#201022890GPV: A 61-year-old female (Switzerland) started Xarelto 10 mg daily on 15-April-2010 (b) (6) after left tibia nail surgery. (b) (6), the patient experienced epidural hematoma (C3-Th8) with very intensive symptoms of temporary paraplegia of both legs (motoric and sensoric) considered serious due to temporary disability. The diagnosis was confirmed by MRI. Additional concomitant medications included Brufen (ibuprofen), Traumanase (bromelains), Magnesium and Tramal (tramadol hydrochloride). Despite several follow-up attempts including bleeding questionnaire, no further information could be obtained. The reporter considered epidural hematoma probably related to Xarelto. Due to the positive temporal relationship and the fact that all anticoagulants might increase the risk of bleeding, especially if taken together with other anticoagulants, the company considers the event as associated to the Xarelto (rivaroxaban), Brufen (ibuprofen) and Traumanase (bromelain) treatment.

MC#2010000014: A 60-year-old female (India) started Xarelto (rivaroxaban) 10 mg daily (b) (6) post knee replacement surgery (b) (6). On the first post-op day in the evening, patient

complained of low back pain. She was treated with analgesics for the event. However the pain did not subside completely. (b) (6), the third post-op day, patient experienced bowel/bladder incontinence. Patient was re-operated and confirmed that an organized EPIDURAL HEMATOMA was responsible for the incontinence. Rivaroxaban was discontinued (b) (6) after about 12 hours of evacuation of the hematoma, bowel/bladder functions were re-gained. The reporting physician considered the events to be related to rivaroxaban. Due to a compatible temporal relationship between the reported event and treatment with Xarelto may increase the bleeding risk on basis of their action mechanism a causal relationship cannot be excluded. The company considers the event as related to Xarelto.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

This reviewer has the following recommendations to each section for the proposed labeling:

- Add a Boxed Warning at the beginning of the label for potential risk of spinal/epidural hematoma in patients who are receiving neuraxial anesthesia or undergoing spinal puncture. This is consistent with the labels given to other anticoagulation products approved with the same indication in patients undergoing hip or knee replacement surgery.
- Indication and Usage (Section 1):
  - Replace "for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism" with specific wording "for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE)" to reflect the study results from the clinical trials.
- Dosage and Administration (Section 2):
  - The recommended treatment duration should be revised from 14 days to 12 days for patients undergoing knee replacement surgery based on submitted clinical data.
- Contraindication (Section 4):
  - Add hypersensitivity as a contraindication
- Warnings and Precaution (Section 5):
  - Add high-risk conditions under the Risk of Bleeding subsection
  - Add a subsection for Renal Impairement to describe the clinical experience and possible risk in this population
  - Add a subsection for Hepatic Impairment to describe the clinical experience and possible risk in this population
  -
- Adverse Reactions (Section 6):

  - Add subcategories for major bleeding in Table 1
  - Include only the most relevant reactions in the table of Adverse Drug Reactions (pruritus, wound healing complications, pain in extremity, increased muscle tone and cramping, wound secreation, blister, syncope, and dysuria)
  - Add a Laboratory Abnormalities subsection to include ALT, AST, total bilirubin, GGT and platelet count results from clinical trials
  - Add a Postmarketing Experience subsection to include other significant events reported from spontaneous reports: cerebral hemorrhage, epidural hematoma, hypersensitivity reactions including anaphylactic shock, agranulocytosis, and Steven-Johnson syndrome.
- Use in Specific Populations (Section 8):
  - Reword the Geriatric Use subsection to comply with 21 CFR 201.57 (c)(9)(v)
- Overdosage (section 10):
  - Reword and delete information that does not apply specifically to rivaroxaban
- Clinical Studies (Section 14):
  - Add important exclusion criteria for the clinical trials
  - Separate proximal DVT and distal DVT in efficacy tables and include results for symptomatic VTE in the tables
  - Delete the sponsor proposed integrated analysis of symptomatic VTE or all-cause death Table
- Patient Counseling Information:
  - Reword to provide specific useful information

9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting for this review cycle.

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/s/

MIN LU
06/03/2011

KATHY M ROBIE SUH
06/03/2011

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 27, 2009

From: Kathy M. Robie Suh, M.D., Ph.D.
Medical Team Leader, Hematology
Division of Medical Imaging and Hematology Drug Products (HFD-160)

Subject: Medical Team Leader Secondary Review/CDTL Review
NDA 22-406, letter date 7/22/08; received 7/28/08
XARELTO^{R} (rivaroxaban) for prophylaxis of deep vein thrombosis (DVT) in patients undergoing hip or knee replacement surgery

To: NDA 22-406

Xarelto (rivaroxaban) Tablets is an orally administered, direct Factor Xa inhibitor being developed for several anticoagulation indications. In this NDA application the sponsor is seeking initial marketing approval of rivaroxaban for the indication:
"for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing:
- hip replacement surgery
- knee replacement surgery"

The proposed dose is 10 mg daily with a treatment duration of up to 35 days.

Background

Venous thromboembolism (VTE) is a major complication of orthopedic surgery during the early post-operative period. Patients undergoing major orthopedic surgery of total hip replacement (THR) or total knee replacement (TKR) are at increased risk for experiencing DVT which may lead to life-threatening or fatal PE. The risk declines with time elapsed after surgery but persists to some extent for at least weeks. Publications have cited venographic rates of deep vein thrombosis (DVT) of approximately 40 to 60% among patients undergoing major orthopedic surgery of the lower limb in the absence of anticoagulation with rates being higher in knee replacement surgery compared to hip replacement. Serious complications of DVT (including pulmonary embolism (PE)) are much less common with generally <1% of events resulting in death. The major risk of thromboprophylaxis is bleeding. Consideration for thromboprophylaxis seeks to balance risk of VTE and risk of bleeding.

Currently there are several agents that are approved and marketed in the U.S. for thromboprophylaxis in orthopedic surgery. These include: Lovenox (enoxaparin sodium)(hip replacement and knee replacement); Arixtra (fondaparinux sodium)(hip replacement, knee replacement, and hip fracture); Fragmin (dalteparin sodium)(hip replacement). All these

products are administered subcutaneously. In addition, heparin sodium is labeled generally for subcutaneous administration for prophylaxis of DVT. Coumadin (warfarin sodium) administered orally is approved generally "for the prophylaxis and/or treatment of venous thrombosis and its extension and pulmonary embolism."

If approved, rivaroxaban would be the first oral anticoagulant approved in the U.S. for the indication being sought and the first oral anticoagulant approved in the U.S. for any indication since approval of warfarin in 1954. Other indications for which phase 2 or 3 clinical investigations of rivaroxaban are ongoing include: for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), for long-term treatment for stroke prevention in patients with chronic atrial fibrillation, for thromboprophylaxis in hospitalized medically ill patients, and in patients with acute coronary syndromes (ACS).

Summary of Studies for Current Indication

The indication currently under review is rivaroxaban 10 mg once daily for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement or knee replacement surgery. This indication is supported by four completed clinical trials, the RECORD Studies. Two of the studies enrolled patients undergoing elective hip replacement and two enrolled patients undergoing elective knee replacement. These studies are described and results presented in detail in the Clinical Review (Min Lu, M.D., M.P.H., completed 3/30/09; signed 4/2/09). Please see Dr. Lu's review for details of study design, efficacy and safety for the application.

All four studies were multinational, randomized, double-blind, double-dummy, parallel groups design. There was an active treatment comparator (enoxaparin) in the control arm of all four studies. The active comparator in the hip replacement studies was a U.S. approved dose regimen of enoxaparin 40 mg once daily beginning 12 hours pre-operatively; however, in one study (RECORD 2) the active comparator was discontinued at day 12 while rivaroxaban was continued to day 35. In the knee replacement studies active treatment duration (12 days) was the same in the two treatment arms in both studies; however, one study (RECORD 3) used an unapproved enoxaparin dose of 40 mg daily beginning pre-operatively as comparator while the other (RECORD 4) used the approved enoxaparin regimen of 30 mg bid beginning 12-24 hours post-operatively. Thus, with regard to fair comparison of rivaroxaban to currently approved treatment for VTE prophylaxis, RECORD 1 would appear to be the most appropriate study for hip replacement surgery and RECORD 4 the most reliable for knee replacement surgery. The major features of study drug treatment in these studies are summarized in Table 1 below.

Table 1: Study Drug Treatment in the Four RECORD Studies

RECORD Study	Daily Dose		Tx Duration (post-op days)	
	Rivaroxaban	Enoxaparin	Riva	Enox
1 (Hip)	10 mg	40 mg[a]	35	35
2 (Hip)	10 mg	40 mg[a]	35	12
3 (Knee)	10 mg	40 mg[a,b]	12	12
4 (Knee)	10 mg	60 mg[c] (30 mg twice daily)	12	12

[a] dosing begun 12 hrs prior to surgery
[b] enoxaparin dose is not FDA-approved for thromboprophylaxis in knee surgery
[c] dosing begun 12-24 hours post-operatively

The primary efficacy parameter, "total VTE" [defined as the composite of: any DVT (proximal and/or distal) or non-fatal PE or death for any reason], was the same for all the studies. Venography at the end of study treatment (post-operative day 36 in the hip replacement studies and day 13 in the knee replacement studies) was used to assess DVT in all four studies. Patients in all four studies were followed for safety for 30 days after last administration of study drug. The primary efficacy endpoint, total VTE, was analyzed at the end of study treatment for the modified intention-to-treat (mITT) population, which consisted of all subjects who received at least one dose of study drug, underwent the surgery and had an adequate assessment of thromboembolism. Important secondary endpoints were the separate components of the primary efficacy endpoint, major VTE events and safety endpoint of major bleeding events.

Subject Disposition and Baseline Characteristics: Subject disposition in the RECORD studies is summarized in the Table 2 below. The great majority of patients in all 4 studies completed the study treatment and completion rates were similar in the two treatment groups in all four studies. Reasons for treatment discontinuation were similar across treatment arms and across studies. Treatment discontinuations due to adverse events were slightly greater in the enoxaparin arms as compared to the rivaroxaban arm in three of the four studies. In each study more patients discontinued study treatment because of reaching a clinical study endpoint. Also, numerically there were more on treatment deaths in the enoxaparin arm in all four studies; however, the numbers were very small.

Table 2: Subject Disposition in RECORD Studies (N, (%))

Group	RECORD 1		RECORD 2		RECORD 3		RECORD 4	
	Riva	Enox	Riva	Enox	Riva	Enox	Riva	Enox
Randomized[a]	2266	2275	1252	1257	1254	1277	1584	1564
Received any study drug	2209 (97.5%)	2224 (97.8%)	1228 (98.1%)	1229 (97.8%)	1220 (97.3%)	1239 (97.0%)	1526 (96.3%)	1508 (96.4%)
Completed treatment	2010 (88.7%)	2011 (88.4%)	1117 (89.2%)	1092 (86.9%)	1127 (89.9%)	1122 (87.9%)	1425 (90.0%)	1413 (90.4%)
Premature termination of study med[b]:	256 (11.3%)	264 (11.6%)	135 (10.8%)	165 (13.1%)	127 (10.1%)	155 (12.1%)	159 (10.0%)	151 (9.6%)
Due to AE	82 (3.6%)	92 (4.0%)	44 (3.5%)	54 (4.3%)	36 (2.9%)	42 (3.3%)	62 (3.9%)	56 (3.6%)
Consent withdrawn	121 (5.3%)	115 (5.1%)	51 (4.1%)	51 (4.1%)	68 (5.4%)	60 (4.7%)	49 (3.1%)	47 (3.0%)
Protocol violation	18	22	26	27	12	21	22	21
Clin endpt	5	11	3	13	5	17	10	18

reached								
Death	1	2	1	3	0	1	1	3
Investigator decision	3	3	2	2	3	5	2	5
LTFU	3	7	2	5	0	2	3	1
Non-Compliant with med	22	12	6	10	3	6	9	0
Technical problem	--	--	--	--	--	--	1	0
Disease progression	--	--	--	--	0	1	--	--
Switch to Commercial med	1	0	--	--	--	--	--	--

[a] randomization was to be done prior to surgery
[b] includes patients who did not receive study med
Riva=rivaroxaban Enox=enoxaparin sodium LTFU=lost to followup
N=number of patients; %=percentage of randomized patients

Because primary efficacy evaluation required blilateral venographic assessment of patients for occurrence of DVT, the primary efficacy population, termed the modified intention-to-treat (mITT) population, was limited to those randomized patients who had received study drug and had adequate venographic evaluation. In these studies 30%-39% of randomized patients were excluded from the mITT population. The extent and reasons for "missing data" (i.e., patients missing adequate assessment of the primary endpoint) were similar between treatment arms in the four studies. Reasons for exclusion of patients from the mITT population are summarized in the following table (Table 3).

Table 3: Summary of Exclusions from the mITT RECORD Study Populations

Group	RECORD 1		RECORD 2		RECORD 3		RECORD 4	
	Riva	Enox	Riva	Enox	Riva	Enox	Riva	Enox
Randomized	2266	2275	1252	1257	1254	1277	1584	1564
Excluded from mITT	671 (30%)	717 (32%)	388 (31%)	388 (31%)	430 (34%)	399 (31%)	619 (39%)	605 (39%)
Reason:								
Inadequate thromboembolism assessment	588 (26%)	635 (28%)	348 (28%)	338 (27%)	376 (30%)	339 (27%)	559 (35%)	546 (35%)
no venography	319 (14%)	322 (14%)	155 (12%)	159 (13%)	156 (12%)	166 (13%)	189 (12%)	184 (12%)
unilateral venography	105 (5%)	105 (5%)	57 (5%)	57 (5%)	82 (7%)	69 (5%)	116 (7%)	105 (7%)
unevaluable venography	121 (5%)	164 (7%)	127 (10%)	111 (9%)	131 (10%)	96 (8%)	244 (15%)	253 (16%)
venography Early/late	43 (2%)	44 (2%)	9 (1%)	11 (1%)	7 (1%)	8 (1%)	10 (1%)	4 (< 1%)

No study drug	57 (3%)	51 (2%)	24 (2%)	28 (2%)	34 (3%)	38 (3%)	58 (4%)	56 (4%)
No surgery	17 (1%)	21 (1%)	16 (1%)	22 (2%)	20 (2%)	22 (2%)	2 (< 1%)	3 (< 1%)

Overall, subjects were enrolled from 41 countries. Approximately 85% of the subjects were enrolled from non-USA sites. Most U.S. patients were enrolled in RECORD 4. This is an important consideration since concomitant medication use and perioperative therapy may vary across countries. Data are not available to fully assess the extent to which USA and non-USA sites may differ in concomitant medication usage (particularly for drugs that increase the risk for bleeding) and operative/perioperative management techniques. Nevertheless, with respect to the number of subjects contributed by any single country, the USA provided the most subjects. Baseline characteristics for patients in the RECORD studies are summarized in the following table. The baseline characteristics generally were reasonably balanced between the rivaroxaban and enoxaparin groups in these studies. The following two tables (Tables 4 and 5) show some of the important baseline characteristics for the safety population and the mITT population.

Table 4: Major Baseline Characteristics in RECORD Studies (Safety population)

Characteristic	RECORD 1 (N=4541)	RECORD 2 (N=)	RECORD 3 (N=2459)	RECORD 4 (N=3034)
Male, %	44.5%	46.4%	31.8%	34.9%
Race, %:				
-white	92.3%	65.0%	81.2%	67.2%
-black	0.9%	2.6%	1.1%	6.0%
-Asian	0.2%	20.0%	6.4%	19.1%
Mean age, years	63.2 yrs	61.5 yrs	67.6 yrs	64.5 years
Age > 75 years	13.0%	13.2%	20.7%	13.8%
Mean weight, kg	78.2 kg	74.8%	80.6 kg	84.6kg
Weight < 50 kg	2.4%	4.9%	1.3%	1.7%
Weight > 110 kg	3.0%	2.7%	3.6%	11.4%
Risk factor for VTE:	8.1%	4.7%	10.9%	5.1%
Active cancer	0.7%	0.6%	0.7%	1.1%
Hx DVT	2.1%	1.1%	3.3%	1.9%
U.S. patients	3.6%	3.2%	0	49.2%

Table 5: Major Baseline Characteristics in RECORD Studies (mITT population)

Characteristic	RECORD 1 (N=3153)	RECORD 2 (N=2509)	RECORD 3 (N=1702)	RECORD 4 (N=1924)
Male	46.1%	48%	33.7%	36.2%
Race:				
-white	93.3%	64%	80.1%	70.4%

-black	0.8%	2%	0.9%	4.7%
-Asian	0.1%	21%	7.8%	15.8%
Mean age, years	62.7 yrs	61.1 yrs	67.6 years	64.5 years
Age > 75 years	11.4%	11.3%	19.4%	14.2%
Mean weight	78.2 kg	74.3 kg	80.5 kg	84.7 kg
Weight < 50 kg	2.4%	5.5%	1.0%	1.7%
Weight > 110 kg	2.8%	2.0%	3.4%	11.5%
Risk factor for VTE	7.7%	3.9%	10.8%	6.2%
Active cancer	0.7%	0.5%	0.6%	1.4%
Hx DVT	1.5%	1.2%	3.2%	2.2%
U.S. patients	3.6%	3.4%	0	50.7%

The major features of the populations were similar for the safety population and the mITT population.

Efficacy Results:
The primary efficacy endpoint in all four studies was a comparison of "Total VTE" rates, defined as the occurrence of: any DVT (proximal and/or distal), non-fatal PE or death due to any cause. All primary endpoint results showed statistically superior results for rivaroxaban ($p < 0.05$), compared to enoxaparin. (As per the statistical plan, superiority test was performed after initial non-inferiority testing in which sponsor's noninferiority margin was met).These primary efficacy results along with the results for the components of the composite endpoint are summarized in Table 6.

Table 6: Primary Efficacy Endpoint ("Total VTE") in RECORD Studies (mITT Population)

Outcome	RECORD 1 (hip)		RECORD 2 (hip)		RECORD 3 (knee)		RECORD 4 (knee)	
	Riva n = 1595	Enox n = 1558	Riva N = 864	Enox n = 869	Riva n = 824	Enox n = 878	Riva n = 965	Enox n = 959
Total VTE	18 (1.1%)	58 (3.7%)	17 (2.0%)	81 (9.3%)	79 (9.6%)	166 (18.9%)	67 (6.9%)	97 (10.1%)
"Total VTE" components								
DVT, all	12 (0.8%)	53 (3.4%)	14 (1.6%)	71 (8.2%)	79 (9.6%)	160 (18.2%)	61 (6.3%)	86 (9.0%)
Nonfatal PE	4 (0.3%)	1 (< 0.1%)	1 (0.1%)	4 (0.5%)	0	4 (0.5%)	5 (0.5%)	8 (0.8%)
Death	4 (0.3%)	4 (0.3%)	2 (0.2%)	6 (0.7%)	0	2 (0.2%)	2 (0.2%)	3 (0.3%)
Components of "DVT, all" (some patients had both proximal and distal DVT)								
Prox DVT	1 (<0.1%)	31 (2.0%)	5 (0.6%)	44 (5.1%)	9 (1.1%)	20 (2.3%)	8 (0.8%)	14 (1.5%)
Distal DVT	12 (0.8%)	27 (1.7%)	11 (1.3%)	49 (5.6%)	74 (9.0%)	156 (17.8%)	57 (5.9%)	82 (8.6%)

Within the knee surgery studies (RECORD 3 and 4) the very great majority of patients with VTE events detected (about 85%) had distal deep vein thromboses. In the hip surgery studies (RECORD 1 and 2) the VTE rates were lower but there still tended to be more distal DVT than other events. Thus, within the individual studies, the rivaroxaban treatment effect was mainly due to differences in the venographic outcomes. Importantly, in all four studies rates of proximal DVT were lower in the rivaroxaban-treated patients than in the enoxaparin groups.

The sponsor conducted an additional secondary efficacy analysis examining occurrence of "Major VTE" which was defined as a composite of: proximal DVT, non-fatal PE or VTE-related death. This analysis was performed using a mITT population that included more patients that the primary efficacy analysis, because some patients had venograms that were evaluable for proximal DVT though not for distal DVT. Rivaroxaban appeared superior to the comparator arm in RECORD 1, 2 and 3 and wih a strng trend in RECORD 4 with result in all 4 studies being driven by venographically detected proximal DVT. This result is shown in Table 7.

Table 7: Main Secondary Endpoint ("Major VTE") in RECORD Studies

Outcome	RECORD 1 (hip)		RECORD 2 (hip)		RECORD 3 (knee)		RECORD 4 (knee)	
	Riva n = 1686	Enox n = 1678	Riva N = 961	Enox n = 962	Riva n = 908	Enox n = 925	Riva n = 1122	Enox n = 1112
Major VTE	4 (0.2%)	33 (2.0%)	6 (0.6%)	49 (5.1%)	9 (1.0%)	24 (2.6%)	13 (1.2%)	22 (2.0%)
"Total VTE" components								
DVT, Proximal	1 (< 0.1%)	31 (1.9%)	5 (0.5%)	44 (4.6%)	9 (1.0%)	20 (2.2%)	8 (0.7%)	14 (1.3%)
Nonfatal PE	4 (0.2%)	1 (0.1%)	1 (0.1%)	4 (0.4%)	0	4 (0.4%)	5 (0.5%)	8 (0.7%)
VTE Death	0	1 (< 0.1%)	0	1 (0.1%)	0	0	1 (0.1%)	0

During the 30-day follow-up period after the end of study treatment, the occurrence of symptomatic VTE events was assessed. In the hip surgery studies 2 rivaroxaban-treated patients experienced events [1 PE, 1 proximal DVT] and 6 enoxaparin–treated patients experienced events [2 PE, 4 proximal DVT and 4 distal DVT]. In the knee surgery studies 8 rivaroxaban-treated patients experienced events [6 PE, 1 proximal DVT, 1 distal DVT] and 6 enoxaparin–treated patients experienced events [4 PE, 1 proximal DVT and 1 distal DVT].

Finally, the sponsor conducted a pre-specified exploratory analysis in the safety population of occurrence of "symptomatic VTE or death" in the pooled patients from all four RECORD studies. Symptomatic events were uncommon but tended to be fewer in the rivaroxaban groups. With the exception of more PE in the rivaroxaban arm in RECORD 1, there were numerically fewer events of symptomatic DVT, PE or death in the rivaroxaban groups as compared to the enoxaparin groups. However, the numbers of events were small and it is not clear that the analysis was planned for hypothesis-testing. No formal statistical method was specified for conducting a meta-analysis of these studies.

Safety results:
In the RECORD studies a total of 12,383 patients were randomized and treated (rivaroxaban, 6183 patients; enoxaparin, 6200 patients). Incidence of any adverse event, treatment-emergent adverse events (within 2 days of drug discontinuation), treatment-emergent serious adverse events, serious adverse events were similar in the rivaroxaban and enoxaparin comparator groups. Adverse events resulting in permanent study drug discontinuation occurred in 3.7% of rivaroxaban treated patients and 4.6% of enoxaparin-treated patients. In the the rivaroxaban group 13 (0.2%) patients died as compared to 25 (0.4%) patients in the enoxaparin group. In the rivaroxaban group 1 death was due to bleeding, 1 was adjudicated as VTE-related and 7 as cardiovascular-related; others were due to sepsis (2), pneumonia, and gastric adenocarcinoma. Among the patients in the enoxaparin groups 1 death was due to bleeding, 2 were adjudicated as VTE-related and 12 as cardiovascular-related; others were due to sepsis (5), pneumonia (2), "acute abdominal distension; elevated transaminases; renal failure; intestinal palsy" (1), and metastatic cancer (1). There were no adjudicated liver-related deaths.

Bleeding: Bleeding is the major anticipated safety concern for rivaroxaban. In the RECORD studies bleeding events were adjudicated by a blinded committee. Treatment-emergent major bleeding (defined as: fatal bleeding, bleeding into a critical organ [e.g., retroperitoneal, intracranial, intraocular or intraspinal], bleeding requiring re-operation, clinically overt extrasurgical site bleeding associated with a decrease in hemoglobin of 2 g/dL or more, or clinically overt extrasurgical site bleeding leading to infusion of 2 or more units of blood) was more common in the rivaroxaban-treated patients than in the enoxaparin-treated patients for both hip and knee surgery studies. Overall, 0.4% of rivaroxaban-treated patients and 0.2% of enoxaparin-treated patients experienced treatment-emergent major bleeding. Bleeding of any degree was experienced by 7.0% of rivaroxaban-treated patients and 6.5% of enoxaparin-treated patients. Bleeding rates were slightly greater in the knee replacement surgery studies (major: rivaroxaban, 0.6%; enoxaparin, 0.4%; any: rivaroxaban, 8.0%; enoxaparin, 7.4%) than in the hip replacement studies (major: rivaroxaban, 0.2%; enoxaparin, 0.1%; any: rivaroxaban, 6.2%; enoxaparin, 5.8%). Number of patients with major bleeding in these studies are summarized in the following table:

Table 8: Numbers of Patients with Major Bleeding in the RECORD Studies (Safety Population)

	Rivaroxaban	Enoxaparin
Total patients with major bleeding:	24	13
Fatal bleeding	2	0
Bleeding into a critical organ	3	5
Bleeding requiring re-operation	12	7
Clinically overt extrasurgical site bleeding associated with a ≥2 g/dL decrease in hemoglobin concentration	8	1
Clinically overt extrasurgical site bleeding requiring transfusion of ≥2 units of whole blood or packed red cells	8	1

Cardiovascular events following treatment discontinuation: A Cardiovascular Events Adjudication Committee adjudicated all deaths in the RECORD studies (with each death

designated as either "cardiovascular" or "noncardiovascular"). The Committee also adjudicated investigator-identified cases of myocardial infarction or stroke.

Overall, the occurrence of cardiovascular events (myocardial infarction, ischemic stroke, cardiovascular death or unexplained death) during treatment or follow-up was uncommon < 1%) within each RECORD study as well as the integrated pool of the studies (0.49% in the rivaroxaban group and 0.63% in the enoxaparin group). During the follow-up period incidence of ischemic stroke in the rivaroxaban group (0.08%) exceeded that in the enoxaparin group (0.02%) with most occurring <10 days post-op hinting at a possibility of an increased tendency for thrombotic events in the early post-operative period. However, rates of these events were low.

Liver Test Abnormalities and Potential Liver Injury: In 2004, the Agency reviewed another oral anticoagulant, ximelagatran, for use in the prophylaxis of deep vein thrombosis in knee replacement surgery, secondary prevention of venous thromboemboli after an acute venous thromboembolus as well as prevention of stroke and other thromboembolic complications associated with atrial fibrillation. That application contained data from patients receiving the drug for short term (treatment duration 7-12 days) (approximately 2225 patients) and long-term (treatment duration ≥6 months) (approximately 4263 patients) clinical studies. The Cardiovascular and Renal Drugs Advisory Committee did not recommend approval, based in large part upon signals of liver toxicity (predominantly in the long term studies), signals of cardiovascular risks (such as myocardial infarction) as well as questionable efficacy in the short term studies. Ximelagatran was not marketed in the USA but was marketed in Europe until the sponsor detected further evidence of liver toxicity in a clinical study of ximelagatran usage during hip surgery. Subsequently, ximelagatran was withdrawn from marketing. Because of this experience, the safety database for rivaroxaban has been examined particularly carefully for possibility of hepatotoxicity.

In the RECORD studies there was a small imbalance between the two treatment groups in the incidence of serious treatment-emergent adverse events alanine aminotransferase (ALT) levels in the RECORD studies (0.27% in the rivaroxaban group and 0.18% in the enoxaparin group). Permanent discontinuation of the study drug reported as due to increased ALT was the same in the two groups (0.11%). In general, this imbalance was not evident in the comparison of the rates of other serious adverse events reported for liver test abnormalities, as shown in Table 20.

Table 9: Incidence Rates of Serious Adverse Events reported for Liver Test Abnormalities in the RECORD Studies (Safety Population)

Event	Rivaroxaban n = 6183	Enoxaparin n = 6200
"Treatment-emergent" (during active treatment period and up to 2 days after last study drug dose)		
Alanine aminotransferase increased	17 (0.27%)	11 (0.18%)
Aspartate aminotransferase increased	5 (0.08%)	6 (0.10%)
Bilirubin increased	5 (0.08%)	4 (0.06%)
Alkaline phosphatase increased	0	1 (0.02%)
"Post-baseline" (at any time point during each study)		

Alanine aminotransferase increased	18 (0.29%)	14 (0.23%)
Aspartate aminotransferase increased	6 (0.10%)	8 (0.13%)
Bilirubin increased	5 (0.08%)	4 (0.06%)
Alkaline phosphatase increased	0	1 (0.02%)

Magnitudes of the elevations of ALT in the RECORD studies were similar between the two treatment groups. Most elevations were greater than 3-times the upper limit of normal but not greater than 5-times the upper limit.

The occurrence of blood ALT > 3X ULN concurrent with total bilirubin > 2X ULN has been proposed as potentially important indicator of drug-induced liver injury ("Hy's law"). Overall, within the pool of completed and ongoing studies (with available data) this outcome occurred in four rivaroxaban-treated patients who subsequently died with liver test abnormalities. The outcome (liver test abnormalities and death) occurred in two comparator group subjects. The patients who died all had comorbid conditions. These cases are described in detail in Dr. Lu's Clinical Review of the application.

Additional review of the safety information in the application relevant to hepatotoxicity was conducted by the Office of Surveillance and Epidemiology (OSE). See "**Additional Information"** section below).

ATLAS Study: This is a recently completed phase 2, open-label, randomized, double-blind, placebo controlled study in patients with acute coronary syndromes. Study enrollment was begun in November 2006, the last patient was enrolled 2/22/08 with last patient visit on 9/19/08 and data lock for the study on 10/18/08. The most recent liver and bleeding safety data from this study were submitted to the Agency on 2/2/09. The full report for this study was recently submitted to the Agency and has not been fully reviewed in this review cycle. In ATLAS patients were randomized 1:1:1 to placebo or rivaroxaban at doses of 5, 10, 15, or 20 mg daily for a treatment duration of 6 months. Dose escalation was done in a sequential fashion and patients were stratified by concurrent treatment with aspirin alone or aspirin plus thienopyridine. The summary data provided suggest a dose-related increased risk for bleeding, as shown in the following table.

Incidence Rates of Treatment-emergent Bleeding-related Adverse Events*, Centrally Adjudicated in the ATLAS ACS TIMI 46 Study

Bleeding Event	Riva 5 mg n = 307	Riva 10 mg n = 1046	Riva 15 mg n = 353	Riva 20 mg n = 603	Placebo n = 1153
Clinically significant	17 (5.5%)	109 (10.4%)	43 (12.2%)	89 (14.8%)	36 (3.1%)
TIMI major	1 (0.3%)	16 (1.5%)	6 (1.7%)	9 (1.5%)	1 (0.1%)
TIMI minor	1 (0.3%)	6 (0.6%)	3 (0.8%)	5 (0.8%)	2 (0.2%)
Requiring medical attention	17 (5.5%)	88 (8.4%)	35 (9.9%)	76 (12.6%)	33 (2.9%)

Definitions for TIMI major and minor bleeding are different from ROCKET studies. TIMI major bleeding = any intracranial bleeding or clinically overt bleeding associated with a decrease in

hemoglobin of ≥ 5 g/dL or an absolute drop in hematocrit of ≥ 15%. TIMI minor bleeding = any clinically overt bleeding associated with a decrease in hemoglobin ≥ 3 g/dL but is < 5 g/dL from the baseline hemoglobin value.

Also, the sponsor provided a comparison of liver test outcomes with pooling of the rivaroxaban cohorts as shown below. Within the study, one patient (placebo group) is reported as experiencing a hepatic-disorder related death.

Incidence of Treatment-emergent Abnormal Liver Test Results in the ATLAS ACS TIMI 46 (all rivaroxaban dose cohorts pooled)

Oucome	Rivaroxaban n = 2302	Placebo n = 1149
ALT > 3X ULN concurrent with total bilirubin > 2X ULN	0	3 (0.3%)
ALT > 3X ULN	55 (2.6%)	37 (3.5%)
ALT > 5X ULN	12 (0.6%)	12 (1.1%)
ALT > 8X ULN	2 (0.1%)	3 (0.3%)
ALT > 10X ULN	1 (< 0.1%)	2 (0.2%)
ALT > 20X ULN	0	0

Ongoing studies: In EINSTEIN DVT/PE study (open-label), 3 cases with ALT> 3xULN concurrent with TB>2xULN (potential Hy's law cases) were reported in the rivaroxaban group (see Table below). One subject had dilated cardiomyopathy and later was transferred to another hospital for terminal care. One subject had cancers and subsequently died. The remaining one subject had acute severe hepatitis with liver failure and subsequently died.

EINSTEIN DVT/PE: ALT >3x ULN Concurrent With TB>2x ULN Cases (All in Rivaroxaban Group)

Age/ sex	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment
77/F White 400011004	169	172	ALT 698/ TB 4.1	Hospitalized for dilated cardiomyopathy (b) (6) Discharged from hospital (b) (6) to another hospital for terminal care. None of these events had resolved as of 3/31/08.	-
63/F 11702-16018-1005	18	18	ALT 5371/ TB 67 mcmol/L	Hospitalized for dyspnea and asthenia (b) (6). Severe acute hepatitis and liver insufficiency was diagnosed on (b) (6). Patient died (b) (6)	Likely drug-induced toxic injury by one member.
71/M White 220131004	35	27	ALT 513/ TB 5.4	Gastric cancer with liver metastasis was found. Subject died (b) (6) No autopsy was performed.	-

In the ROCKET-AF Study (rivaroxaban vs. warfarin) 16 subjects with ALT>3xULN concurrent with TB>2xULN have been reported and 3 cases have been reported in the J-ROCKET-AF Study. Both studies are blinded studies. Two of the ROCKET-AF cases have been unblinded and both had received warfarin. One case in the J-ROCKET-AF study has been unblinded and had received rivaroxaban. Three subjects in ROCKET-AF study have died and these cases remain blinded.

Additional Information:
Advisory Committee: The rivaroxaban application was presented and discussed on March 19, 2009 at a meeting of the FDA Cardiovascular and Renal Drugs Advisory Committee. Some results from the recently completed ATLAS study were presented by the sponsor. For the question of "Do the available clinical data demonstrate a favorable risk-benefit profile for rivaroxaban in the prophylaxis of VTE in patients undergoing hip or knee replacement surgery?" the Committee voted 15 (yes) to 2 (no). One member voted "no" due to concerns for potential for severe hepatotoxicity and the other had concerns for bleeding and overall benefits of rivaroxaban. During discussion, committee members expressed varying levels of concern about the strength of the signals for hepatotoxicity and the feasibility of long term studies to further elucidate the hepatotoxicty seen with rivaroxaban. There were no objections from the committee members for approval without the data from the on-going "long term" atrial fibrillation studies. However, most members stated that longer term studies in identified populations are needed. In regard to whether a lower dose than 10 mg should be available for special populations based PK/PD studies, the committee voted 5 (Yes) to 9 (No) (abstain 3). Many committee members expressed that there was not enough data to support a lower dose. While some were persuaded that there might be a loss of efficacy others expressed concerns for safety in these specific patient populations.

Office of Safety and Epidemiology (OSE): Office of Safety and Epidemiology review evaluated the application for evidence of hepatotoxicity (K. Gelperin, Division of Epidemiology (DEPI), OSE, 2/13/09). The review concluded that "There does not appear to be a high risk of severe liver injury during the short-term use (<12 days) of ximelagatran relative to warfarin. However, the risk of severe liver injury for the shortterm use has not been fully characterized." The review recommended that if approved the labeling for rivaroxaban should include strong measures, such as a boxed warning limiting the duration of ximelagatran therapy to 12 days of therapy to avoid risk of severe drug-induced liver injury while acknowledging that this restriction "does not provide assurance that a delayed-onset of injury after cessation of exposure cannot occur with this drug". Division of Risk Management (DRISK), OSE evaluation recommended that a formal risk management program with safe use strategies should be considered *if* the data identify the at-risk subpopulation and/or a monitoring approach that will prevent serious adverse hepatobiliary events. However, the review commented that in the absence of such directive information, it is not likely that any risk management program will be effective minimizing hepatotoxicity. (K. O'Connell, M.D., Ph.D., 2/12/09).

Division of Scientific Investigations (DSI): Though the application is submitted by Johnson & Johnson, the pivotal RECORD studies for the NDA submission were conducted by Bayer. Findings of DSI inspection of several sites show evidence of questionable sponsor monitoring at

several clinical sites and issues such as underreporting of adverse events at some sites. Of particular concern is that some of the sites of concern are in the RECORD 4 study which had the largest contribution of U.S. subjects among the studies. (See Memorandum from S. Thompson, DSI, 5/15/09)

Pediatrics: Knee replacement and hip replacement surgery are rare in pediatric patient so study of rivaroxaban for the current indication being sought is not relevant to the pediatric population. However, because the drug is under development for other indications, such as treatment of VTE which are applicable to pediatric patients, DMIHP requested comment from the Pediatric and Maternal Health Team on the feasibility of studying rivaroxaban for any use in pediatric patients. That review concluded: "Although uncommon, the incidence of thromboembolic events in children are increasing and adequate and well controlled studies of anticoagulant drug products would produce health benefits for the pediatric population by providing information about the safety and efficacy of these drugs. Based on the literature and knowledge of ongoing trials, an adequate number of pediatric patients with VTE appear to be available for study." However, any such investigation should await establishment of safety and efficacy in adult patients. (E. Durmowicz, M.D., 4/29/09).

Chemistry, Manufacturing and Controls (CMC): Chemistry review of the application found outstanding deficiencies that precluded CMC recommendation for approval of the application. Important issues identified by Chemistry review included: problems with dissolution specifications, inadequate information about the drug substance, significant DMF deficiencies and issues regarding the proposed labels (T. Ghosh, Ph.D., 3/31/09; J. M. Jee, 5/12/09).

Clinical pharmacology: Review of clinical pharmacology studies for rivaroxaban was done by J. Grillo, 4/2/09). Rivaroxaban produces a maximum blood concentration 2 to 4 hours following oral ingestion of the dose. The drug is highly bound to blood albumin in humans (92% to 95%) and approximately two-thirds of the drug undergoes metabolic degradation, with half eliminated renally and the other half eliminated by the fecal route (liver metabolism and/or gastrointestinal transit). The remaining one-third of the administered dose undergoes direct renal excretion as unchanged active substance. Elimination of rivaroxaban from plasma occurs with a terminal half-life of 5 to 9 hours in young individuals and with a terminal half-life of 11 to 13 hours in the elderly. (No specific antidote is available for reversal of the anticoagulant effect of rivaroxaban).

Rivaroxaban prolongs the blood prothrombin time (PT) and activated partial thromboplastin time (aPTT) although monitoring of these laboratory tests are not proposed for use during rivaroxaban therapy. The exposure-response data indicate a more shallow curve for anticoagulant effect than for bleeding, indicating that bleeding risk increases more rapidly than does antithrombotic effect as exposure is increased.

The clinical pharmacology of rivaroxaban is particularly notable for its dual pathway of elimination. Within the liver, the drug undergoes oxidative degradation by the cytochrome P450 enzyme system (specifically CYP3A4/5 and CYP2J2). Alteration of one or both these pathways by patient-specific factors (such as liver or renal disease) and/or the concomitant use of certain medications may importantly increase blood rivaroxaban concentrations. This increased rivaroxaban exposure, in turn, may increase the risk for bleeding.

With respect to active renal excretion, *in vitro* studies have shown rivaroxaban is a substrate of the transporter protein, P-gp, and breast cancer resistance protein (Bcrp). Consequently, co-administration of rivaroxaban with drugs that are moderate to strong inhibitor drugs of certain cytochrome P450 enzymes and/or the P-gp transporter (such as ketoconazole and ritonavir) will block both elimination pathways for rivaroxaban and may result in clinically relevant increases in plasma rivaroxaban levels and may increase the risk for bleeding. A similar concern exists when these drugs are used in patients with preexisting renal and hepatic disease since both elimination pathways are affected and a greater than additive increase in exposure is possible.

There may be a synergistic potential for bleeding associated with co-administration of rivaroxaban and other drugs that also affect coagulation. Limited data have signaled a prolongation of the bleeding time during concomitant rivaroxaban and clopidogrel therapy, even though clopidogrel did not alter rivaroxaban phamacokinetics.

Because of the concerns for increased exposure and therefore increased bleeding risk in certain patients, it may be necessary for the sponsor to develop a lower dose (e.g., 5 mg) tablet or scored 10 mg tablet to permit downward dose titration in the these special populations.

Review of a thorough QT study found no significant QT prolongation effect of BAY 59-7939 (15 mg and 45 mg) (J. Zhang, Interdisciplinary Review Team for QT Studies, 3/4/09).

Pre-Clinical: Non-clinical studies did not reveal organ-specific toxicity. Dog studies (up to 12 months exposure) showed that rivaroxaban produced anticoagulation, with the major toxicity related to hemorrhage. In rats, overt bleeding was not observed up to the highest tested dose. Pharmacology review of the pre-clinical studies for rivaroxaban recommended the application for approval from a pharmacology/toxicology perspective (Y. Chopra, 5/12/09)

Foreign marketing: Rivaroxaban was approved for marketing in Europe in September, 2008. As of December 5, 2008, adverse event reports (two patients) have pertained to bleeding events (non-fatal).

Discussion:
The sponsor's background package for their Advisory Committee presentation cites studies (Friedman 2008 and Cohen 2008) indicating that 90-95% of THR and TKR patients are receiving some form of postoperative prophylaxis. They indicate further that "A review of 30,714 consecutive selective hip procedures at the Mayo Clinic over the period from 1969 to 1997 showed that the 30-day death rates declined from 0.94% in the 1970's to a stable rate of 0.15% in the 1990's." Thus, the need for thromboprophylaxis in the orthopedic surgery setting largely appears to be being met by the currently available therapeutic options. Therefore, it is not likely that approval of another agent for this use will affect the overall impact of major orthopedic-associated VTE on public health. The uptake of rivaroxaban for the indication will most likely merely result in the shift of patients from established agents to the newer agent with the main clinical benefit being convenience of oral administration (as opposed to subcutaneous administration) in the outpatient setting. Based on the above information from the Mayo Clinic, with current medical practice (which includes thromboprophylaxis in the vast majority of THR

and TKR surgeries) there is 1 death for approximately 667 patients undergoing the surgery. It seems reasonable, then, that a new treatment should evidence a safety profile with a similarly very low or lower rate of life-threatening adverse reactions as the existing treatments. The sponsor indicates that rivaroxaban increases the risk of major bleeding (fatal bleeding, bleeding into a critical organ, bleeding requiring re-operation, clinically overt extrasurgical site bleeding associated with a $\geq$2 g/dL decrease in hemoglobin concentration, and clinically overt extrasurgical site bleeding requiring transfusion of $\geq$2 units of whole blood or packed red cells) by 0.18% (rate of 0.39% with rivaroxaban as compared to 0.21% with enoxaparin in the RECORD studies). The major bleeding events with the treatments in these studies were as shown in the table below:

The above numbers suggest that in practice clinically important serious bleeding, including fatalities and re-exposure to surgical intervention, is likely to be more common with rivaroxaban than with enoxaparin.

The other major safety concern with rivaroxaban, namely possible hepatotoxicity, is more difficult to assess using the available database. It is generally accepted that concurrent elevations of ALT greater than 3 times upper limit of normal and of total bilirubin greater than 2 times upper limit of normal portend serious hepatic injury. (See FDA "Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (October 2007)). In the RECORD studies, such occurrences after starting study drug were fairly uncommon [7 subjects (0.11%) receiving rivaroxaban (6131 patients exposed) and 7 subjects (0.11%) receiving enoxaparin (6131 patients exposed)]. For the total safety database from all clinical studies as of 12/5/08 (20320 subjects with any exposure to rivaroxaban), 4 subjects (0.02%) who died had an ALT greater than 3 times upper limit of normal and total bilirubin greater than 2 times upper limit of normal 30 days prior to death. Stopping rules for hepatotoxicity stipulated permanent discontinuation of treatment of treated patients having specifically defined sustained elevations of ALT and bilirubin; however, these rules resulted in permanent discontinuation of relatively few patients--- 7 each rivaroxaban and enoxaparin (rivaroxaban: 4, 0, 2, 1; enoxaparin : 2, 3, 0, 2, for RECORD studies 1, 2, 3 and 4, respectively). In both treatment groups the occurrence of ALT elevation greater than 3 times upper limit of normal was much more common --- 152 patients (2.48%) in the rivaroxaban group and 227 patients (3.7%) in the enoxaparin group. The impact, if any, of these ALT elevations on the management of these patients is not clear from the datasets and analyses presented. Furthermore, it is not known whether the significance of hepatic enzyme elevation due to rivaroxaban has the same clinical import as elevations due to enoxaparin. Because enoxaparin as well as the other low molecular weight heparins and unfractionated heparin as well can cause transient and apparently benign elevation of hepatic transaminases, between treatment group comparison of hepatic toxicity in the RECORD studies is particularly difficult. Importantly, the recent DSI report of irregularities at some RECORD study sites raises further concerns that the blinding of the study may not have been intact at some sites and that at some sites certain aspects of conduct of the study may not have been done in adherence to the stipulated protocol procedures, even though the sponsor may have been aware of the deviations. Thus, based on the available data it is not possible to reasonably assess the significance of the liver toxicity signal in the rivaroxaban treated patients.

Conclusions and Recommendations:

Barring gross irregularities in the conduct of the RECORD studies, it seems reasonably clear that rivaroxaban has efficacy as an anticoagulant for thromboprophylaxis in the settings of elective hip replacement and knee replacement surgery as assessed, based on the accepted endpoint of "total VTE" [composite of any DVT, non-fatal PE or death]. It is not clear that rivaroxaban is more effective than enoxaparin used optimally. The Statistical review (Q Xu, Ph.D., 5/8/09) found convincing evidence for efficacy based on the primary efficacy endpoint and stated for the efficacy analyses that "Findings from using different approaches to deal with missing data issues with the primary endpoint consistently concluded the robustness of the primary efficacy results." For secondary efficacy analyses and pooled analysis results were not convincing, with the exception of indicating that the predominant effect on the primary efficacy endpoint was on the component of asymptomatic venographically-detected DVT. While the data (if valid) support efficacy of rivaroxaban, they do not support a claim of superiority of rivaroxaban over enoxaparin for this use. The study results (if valid) provide support for rivaroxaban as decreasing the rate of proximal as well as distal DVT in these clinical settings. However, the studies do not provide convincing evidence for rivaroxaban as decreasing the rate of symptomatic VTE events in these settings.

The safety data suggest that rivaroxaban may cause somewhat greater rates of bleeding, including major bleeding, than enoxaparin. Any use of rivaroxaban should consider the balance of the risk of VTE versus that of major bleeding for the particular patient. Furthermore, a risk for hepatotoxicity with rivaroxaban cannot be ruled out at this time. This is of particular concern since though this initial NDA submission is for a short-term indication already well-addressed by currently available medications, the most logical market for rivaroxaban, an oral anticoagulant that does not require monitoring for dose adjustment for treatment effect, is for long-term use in chronic diseases where life-long thromboprophylaxis is needed, e.g., chronic atrial fibrillation. It would be prudent to further investigate this risk prior to marketing approval of rivaroxaban, possibly by awaiting results of longer-term treatment studies of rivaroxaban.

This application has undergone thorough review and evaluation by all relevant disciplines. (See Additional Information section above). The deficiencies and recommendations of those reviews should be conveyed to the sponsor.

At present information is inadequate to make detailed recommendations for the labeling for the application. However, if approved the rivaroxaban label should reflect risk of bleeding, what is known about hepatotoxicity, and the label should provide language to limit the duration of treatment with the drug to that studied in the trials relevant to the indication. Consideration should be given to measures to control marketing of the product to enhance likelihood of compliance with the treatment duration limit.

The most appropriate recommendation for regulatory action at this time is "complete response". In issuing a complete response for a clinical viewpoint critical major deficiencies listed should include, inadequate evaluation of the potential for hepatotoxicity for the product and need for a thorough inspection of the completed and ongoing clinical studies of rivaroxaban to provide assurance of data integrity, completeness and appropriate oversight of the conduct of the studies. Also, the major deficiences indicated in the discipline reviews should be included.

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/s/

Kathy Robie-Suh
5/27/2009 03:26:38 PM
MEDICAL OFFICER

Summary Review for Regulatory Action

Date	May 12, 2009
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA#	22-406
Applicant Name	Johnson and Johnson Pharmaceutical Research and Development, LLC
Date of Submission	July 22, 2008
PDUFA Goal Date	May 28, 2009
Proprietary Name / Established (USAN) Name	XARELTO™ Rivaroxaban
Dosage Forms / Strength	Film-coated 10 mg tablet for oral intake
Proposed Indication(s)	"XARELTO (rivaroxaban) is indicated for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolus (PE) in patients undergoing: - hip replacement surgery - knee replacement surgery."
Action/Recommended Action for NME:	Complete Review (request for clarifying chemistry, manufacturing and control data, clinical data and data verifying clinical data integrity).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Min Lu, MD & Kathy Robie Suh, MD PhD (TL)
Statistical Review	Qing Xu, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Yash Chopra, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Joesphine Jee, PhD & Sarah Pope, PhD (Leader)
Microbiology Review	Not applicable
Clinical Pharmacology Review	Joseph Grillo, PhD & Young Moon Choi, PhD (TL)
DDMAC	Michelle Safarik, PA-C
DSI	Susan Thompson, MD & Tejashri Purohit-Sheth, MD
CDTL Review	Kathy Robie Suh, MD, PhD
OSE/DMEPA	Eselaine Jones Smith PharmD and Kristina Arnwine, PharmD
OSE/Epidemiology Division	Kate Gelperin, MD & John Senior, MD
OSE/DRISK	Kathryn O'Connell, MD, PhD, Claudia Karwoski, PharmD
Pediatric and Maternal Health	Karen Feibus, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DSRCS=Division of Surveillance, Research, and Communication Support
DRISK=Division of Risk Management

CDTL=Cross-Discipline Team Leader
TL = Team Leader

1. Introduction:

This New Drug Application (NDA) was submitted for rivaroxaban (XARELTO), an anticoagulant proposed for use in the prevention of DVT/PE among patients undergoing hip or knee replacement (see above). Rivaroxaban is thought to act as an anticoagulant through inhibition of factor Xa activity. This inhibition culminates in inhibition of thrombin formation and blackade of the coagulation cascade.

Overall, the applicant provides convincing evidence of rivaroxaban efficacy. However, data are insufficient to verify safety and, to date, clinical data integrity have not been verified. Additionally, manufacturing deficiencies remain. This review will focus upon the regulatory basis for this first review cycle's recommendation for submission of a Complete Review letter to the NDA sponsor.

Because the ultimate regulatory action for this review cycle has been determined, I am creating this review at a time point when the final reviews for certain disciplines (chemistry, CDTL, PT) are pending. Additionally, the final establishment inspection report will be available only shortly prior to the action due date. I will amend this review document following my examination of these final reviews.

2. Background:

Currently, four drugs are approved by the FDA for use in the prevention of venous thromboembolism (VTE) in the setting of hip and/or knee replacement surgery. These drugs are all administered parenterally (enoxaparin, fondaparinux, dalteparin and unfractionated heparin). The only FDA-approved oral anticoagulant, warfarin, is not specifically indicated for use in the prevention of VTE in the perioperative period but publications have cited its use in this setting.

Multiple oral anticoagulants are under clinical development and one (ximelagatran) was the subject of an NDA reviewed at an advisory committee in 2004 and a non-approval action by the FDA. The ximelagatran NDA was submitted to support the drug's use in the prevention of VTE associated with hip surgery as well as the prevention of thrombotic complications among patients with atrial fibrillation. In this development program, the hip surgery studies were referred to as "short term" studies because the study drug was administered for only several days while the atrial fibrillation studies were referred to as "long term" studies because the study drug was administered for many months (and intended for life-long administration).

The "long term" ximelagatran studies showed evidence of important liver toxicity whereas this toxicity was not readily evident in the "short term" clinical studies. Additionally, the ximelagatran efficacy data were assessed as equivocal. For these reasons, ximelagatran was not approved in the US. The drug was approved for the "short term" indication in other countries. Ultimately, ximlegatran was removed from world-

wide marketing because severe liver toxicity appeared among some patients who had received only a few days of ximelagatran.

Ximelagatran has no structural similarities to rivaroxaban and the ximlegatran experience is relevant to rivaroxaban mainly to exemplify the importance of both "short term" and "long term" clinical studies in assessing an oral anticoagulant's activity since almost all oral anticoagulants are under development for both short and long term usages. Unlike the original ximelagatran NDA, this original rivaroxaban NDA was submitted only with "short term" clinical study data.

Rivaroxaban is unique, in comparison to warfarin, because the use of rivaroxaban does not require anticoagulant parameter monitoring (e.g., PT/INR) and the proposed rivaroxaban dose is the same for all patients (no dose titration). Rivaroxaban does prolong the PT/INR but this prolongation has not been convincingly correlated with the drug's anticoagulant effectiveness.

Rivaroxaban is currently under development in five major indication/areas:

- VTE prevention in hip or knee replacement surgery
- Secondary prevention of VTE following an index event
- VTE prevention among "hospitalized, medically ill" patients
- Prevention of thrombotic complications of atrial fibrillation
- Prevention of certain ischemic complications among patients with an acute coronary syndrome (ACS)

3. Chemistry, Manufacturing and Controls (CMC):

The review of the CMC aspects of this NDA was somewhat complicated by the location of all the manufacturing information in drug master files, which were not sponsored by the NDA applicant. The CMC reviewers have identified many deficiencies within these drug master files and the applicable sponsors have not resolved these deficiencies.

4. Nonclinical Pharmacology/Toxicology:

At the present time the nonclinical pharmacology/toxicology review is pending. Based upon midcycle discussion and subsequent discussions, no deficiencies are anticipated.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The reviewer provides some recommendations for labeling as well as a recommendation for a post-marketing requirement to develop a 5 mg tablet (or scored 10 mg tablet) for use among patients at risk for clinically relevant changes in rivaroxaban exposure.

During the review, considerable discussion focused upon the exposure-response considerations for patients with renal or hepatic insufficiency as well as patients who were receiving certain drugs that alter rivaroxaban metabolism/elimination. Rivaroxaban is eliminated through both renal and hepatic routes and altered function of these organs can lead to increased rivaroxaban exposure.

6. Clinical Microbiology:

Not relevant for an orally administered tablet.

7. Clinical/Statistical-Efficacy:

Dr. Min Lu provided the primary clinical review and Dr. Kathy Robie Suh is developing the secondary/CDTL review. Dr. Lu was the lead medical officer assigned to rivaroxaban throughout its development and has become very familiar with the drug's clinical manifestations. I have read Dr. Lu's review and concur with her recommendations that the sponsor provide the following information:

1) A report of a safety monitoring board's review of the case reports for patients with certain liver test abnormalities (serum ALT > 3X ULN with serum total bilirubin > 2X ULN) in the on-going ROCKET-AF studies. This review should focus upon the detection of any important signal for rivaroxaban liver toxicity, based upon an imbalance in the occurrence of these events between the study groups as well as the clinical characteristics of the individual subjects. The information should be provided to the FDA in a manner that preserves the integrity of the on-going clinical study.

2) The complete ATLAS ACS TIMI 46 study report. This study compares rivaroxaban to placebo over a six month exposure time. The study purportedly shows no evidence of rivaroxaban liver toxicity and the NDA applicant presented this information to the advisory committee we convened to review rivaroxaban. At this point in time, the NDA applicant tells us the final study report will be submitted within the next few days. Because this submission will not change the ultimate regulatory action for this review cycle, we will not review the ATLAS ACS TIMI 46 study during this review cycle.

3) A report of the safety findings from the rivaroxaban post-marketing experience outside the US. This report should include tabular and text summaries of spontaneously reported adverse events and an estimate of the numbers of patients exposed in the market place.

4) A status update and summary of adverse events from any post-marketing studies.

Overall, clinical data from approximately 18,000 subjects were submitted in this NDA, including data from 12,729 patients enrolled in the four main phase 3 clinical studies. These clinical studies are referred to as the "RECORD" studies (Regulation of coagulation in orthopedic surgery to prevent DVT and PE) and, for simplification are referred to as:

RECORD 1 and 2: examined hip surgery setting
RECORD 3 and4: examined knee surgery setting

All four studies shared several design characteristics: all were randomized (1:1) comparisons to enoxaparin, double blinded, international studies in which patients were to undergo venography on day 12 (knee setting) or day 35 (hip setting). The rivaroxaban dose was 10 mg and was administered for 12 (knee) or 35 days (hip). Rivaroxaban was started 6 to 8 hours post-operatively. All patients underwent one month of (off drug) follow-up.

The RECORD studies had a few important differences that confound any efforts to "pool" clinical data in order to form conclusions:

-in RECORD 3, the enoxaparin dose (40 mg daily) was one that has not been approved in the US and is of unverified efficacy

-in RECORD 2, rivaroxaban was administered for 35 days while enoxaparin was administered for only 12 days; since the primary endpoint was determined at 35 days, the imbalance in study drug administration reflects a difference in treatment regimens, not solely the study drugs.

The primary endpoint in the RECORD studies was a composite referred to as "Total VTE" and consisted of: death for any cause, non-fatal PE or DVT. The DVT outcome could be asymptomatic (based on venogram) or symptomatic (verified). Adjudication boards reviewed all primary endpoint events and also reviewed all bleeding events (to classify bleeding events into specific categories, such as "major" or "non-major").

Overall, compliance with the study plans was solid, with approximately 90% of all enrolled subjects completing the RECORD studies. However, compliance with the venography expectations was limited and approximately 30% of the subjects did not undergo venography. This relatively low venography compliance rate is similar to that detected in many other clinical studies, including studies used to support the approval of currently marketed drugs.

The primary endpoint results are shown below, along with the components of the "Total VTE" composite. The primary endpoint was prespecified to be analyzed among the per-protocol population for non-inferiority and the modified ITT population for superiority. Because all primary endpoints ultimately met the non-inferiority tests, in the summaries we highlighted only the superiority tests of the primary endpoint. The modified ITT population which was defined as the group of subjects who received at least one dose of study drug, underwent the surgery and had an adequate assessment of thromboembolism.

Table 1. Primary Endpoint ("Total VTE") in RECORD Studies

Outcome	RECORD 1 (hip)		RECORD 2 (hip)		RECORD 3 (knee)		RECORD 4 (knee)	
	Riva n = 1595	Enox n = 1558	Riva n = 864	Enox n = 869	Riva n = 824	Enox n = 878	Riva n = 965	Enox n = 959
Total VTE*	18 (1.1%)	58 (3.7%)	17 (2.0%)	81 (9.3%)	79 (9.6%)	166 (18.9%)	67 (6.9%)	97 (10.1%)
"Total VTE" components								
DVT, all	12 (0.8%)	53 (3.4%)	14 (1.6%)	71 (8.2%)	79 (9.6%)	160 (18.2%)	61 (6.3%)	86 (9.0%)
Nonfatal PE	4 (0.3%)	1 (< 0.1%)	1 (0.1%)	4 (0.5%)	0	4 (0.5%)	5 (0.5%)	8 (0.8%)
Death	4 (0.3%)	4 (0.3%)	2 (0.2%)	6 (0.7%)	0	2 (0.2%)	2 (0.2%)	3 (0.3%)
Components of "DVT, all" (some patients had both proximal and distal DVT)								
Prox DVT	1 (<0.1%)	31 (2.0%)	5 (0.6%)	44 (5.1%)	9 (1.1%)	20 (2.3%)	8 (0.8%)	14 (1.5%)
Distal DVT	12 (0.8%)	27 (1.7%)	11 (1.3%)	49 (5.6%)	74 (9.0%)	156 (17.8%)	57 (5.9%)	82 (8.6%)

*all p-values for comparison of rates < 0.05 (Mantel-Haenszel-weighted difference)

Table 1 shows that, within the individual studies, the rivaroxaban treatment effect was mainly due to differences in the venographic outcomes, with a reduction in the rates of both proximal and distal DVT.

The "main" secondary endpoint was "Major VTE" which was defined as a composite of: proximal DVT, non-fatal PE or VTE-related death. In RECORD 1, 3 and 4, this endpoint was analyzed in a step down procedure (non-inferiority/followed by superiority), similar to the primary endpoint. For this main secondary endpoint, superiority for rivaroxaban was shown in RECORD 1, 2 and 3 but not in RECORD 4 (mITT population). However, in RECORD 4, the rivaroxaban rate was below the treatment difference non-inferiority limit of 1.5%, suggesting non-inferiority.

Overall, the main secondary endpoint suggested that the major rivaroxaban treatment effect related to a reduction in proximal DVT detected on venography (Table 2).

Table 2. Main Secondary Endpoint ("Major VTE") in RECORD Studies

Outcome	RECORD 1 (hip)		RECORD 2 (hip)		RECORD 3 (knee)		RECORD 4 (knee)	
	Riva n = 1686	Enox n = 1678	Riva n = 961	Enox n = 962	Riva n = 908	Enox n = 925	Riva n = 1122	Enox n = 1112
Major VTE*	4 (0.2%)	33 (2.0%)	6 (0.6%)	49 (5.1%)	9 (1.0%)	24 (2.6%)	13 (1.2%)	22 (2.0%)
"Total VTE" components								
DVT, Proximal	1 (< 0.1%)	31 (1.9%)	5 (0.5%)	44 (4.6%)	9 (1.0%)	20 (2.2%)	8 (0.7%)	14 (1.3%)
Nonfatal PE	4 (0.2%)	1 (0.1%)	1 (0.1%)	4 (0.4%)	0	4 (0.4%)	5 (0.5%)	8 (0.7%)
VTE Death	0	1 (< 0.1%)	0	1 (0.1%)	0	0	1 (0.1%)	0

*p-values for comparison of rates < 0.05 (Mantel-Haenszel-weighted difference) in RECORD 1, 2 and 3; in RECORD 4 p-value = 0.12

Multiple other secondary endpoints were analyzed within the individual RECORD studies. The numbers of patients with symptomatic VTE events was relatively small within each study, with numerically lower rates reported for patients in the rivaroxaban groups, but nominal statistical significance evident only in the RECORD 2 and 3 studies. During the follow-up (post-therapy) period, the occurrence of symptomatic VTE events remained uncommon in each RECORD study. In general, the rates during this period were similar between the rivaroxaban and enoxaparin groups in each study.

Of particular note were the prespecified integrated analyses for the RECORD studies. It is not clear that the analysis was planned for confirmatory hypothesis-testing. The primary endpoint in these analyses was a comparison of the rates of symptomatic VTE (DVT and/or PE) or death from all causes (which ever comes first) during the treatment period of the studies. The endpoint was analyzed as a time to event comparison using a Cox regression model with study (RECORD 1, 2, 3 and 4) and treatment group as covariates to determine the hazard ratios for the primary endpoint and the corresponding 95% CI. The analytical population consisted of all patients who received at least one dose of study drug (the "safety population").

A summary of the rates of symptomatic VTE or death during the treatment phase of each of the RECORD studies is shown in the following table.

Table 3. "Symptomatic VTE or Death" in RECORD Studies (safety population)

Out-come	RECORD 1 (hip)		RECORD 2 (hip)		RECORD 3 (knee)		RECORD 4 (knee)	
	Riva n = 2209	Enox n = 2224	Riva n = 1228	Enox n = 1229	Riva n = 1220	Enox n = 1239	Riva n = 1526	Enox n = 1508
Any event	10 (0.5%)	15 (0.7%)	5 (0.4%)	20 (1.6%)	8 (0.7%)	26 (2.1%)	12 (0.8%)	21 (1.4%)
*Components of "Symptomatic VTE or Death" Endpoint**								
DVT	3 (0.1%)	9 (0.4%)	2 (0.2%)	10 (0.8%)	8 (0.7%)	20 (1.6%)	6 (0.4%)	10 (0.7%)
PE	4 (0.2%)	2 (0.1%)	1 (0.1%)	5 (0.4%)	0	4 (0.3%)	5 (0.3%)	8 (0.5%)
Death	4 (0.2%)	5 (0.2%)	2 (0.2%)	3(+3)^ (0.5%)	0	2 (0.2%)	2 (0.1%)	3 (0.2%)

*some patients could have both a PE and DVT

^ 3 of 6 deaths occurred during the placebo treatment period

The Sponsor's integrated summary (all 4 studies combined) is shown in Table 4.

Table 4. Sponsor's Integrated Summary of "Symptomatic VTE or Death" in RECORD Studies (safety population; active treatment period)

Outcome	Rivaroxaban n = 6183	Enoxaparin n = 6200	Hazard Ratio, point estimate and 95% CI	p-value
VTE/Death	35 (0.6%)	82 (1.3%)	0.42 (0.29 - 0.63)	< 0.05
VTE (DVT &/or PE)	28 (0.5%)	68 (1.1%)	0.41 (0.26 - 0.64)	< 0.05
PE	10 (0.2%)	19 (0.3%)	0.53 (0.24 - 1.13)	0.10
Death	8 (0.1%)	13 (+3)^ (0.3%)	0.50 (0.21 - 1.17)	0.11

^ 3 of the deaths occurred during the placebo treatment period in RECORD 2 study

Although, it appears that twice as many deaths were reported in the enoxaparin group as in the rivaroxaban group, it must be noted that 5 of the 8 excess deaths attributed to the enoxaparin group either occurred during the placebo-controlled period of RECORD 2 study or occurred in the RECORD 3 study with lower enoxaparin dose. Overall, the numbers of death were too small to show a nominal statistically significant difference between the two groups. Determining the cause of death is vulnerable to considerable

error. Nevertheless, the investigators assessed pulmonary emboli as the cause for death in thee patients in the rivaroxaban group and the cause of death in two enoxaparin group patients.

The FDA statistical review of integrated analyses suggested that the sponsor's pre-specified statistical analysis plan for the pooled analyses was that of the exploratory nature with no adjustments to the significance levels to account for multiple comparisons on the same data or for multiple efficacy variables. Another issue was the "poolability" of the data from all 4 RECORD studies. As noted before, RECORD 2 study used shorter duration of enoxaparin and RECORD 3 study used lower (unapproved) dose of enoxaparin. Therefore simple pooling of data from all four studies without any adjustment may lead to biased comparison with underestimated effect of enoxaparin. The FDA statistical reviewer conducted several sensitivity analyses to address this issue and concluded that the "pooling" was inappropriate for making labeling claims or solid conclusions.

Overall, the sponsor's data provide convincing evidence of rivaroxaban efficacy, based predominantly upon asymptomatic thrombi detected on venograms (an "accepted" marker for efficacy in this indication). Additionally, multiple exploratory analyses support rivaroxaban's efficacy. While the "pooling" data are suggestive of "clinical" benefit, these data are exploratory in nature and not appropriate for labeling claims.

8. Safety:

Overall, the major safety considerations related to bleeding (rivaroxaban was shown to be associated with more bleeding that enoxaparin) and signals for liver toxicity (the signals were equivocal). Hypothetical concerns for an increased risk of thrombotic events following rivaroxaban discontinuation were not confirmed in the studies.

For the combined safety database for these four studies a total of 12,383 patients were randomized and treated (rivaroxaban, 6183 patients; enoxaparin, 6200 patients). Incidence of any adverse event, treatment-emergent adverse events (within 2 days of drug discontinuation), treatment-emergent serious adverse events, serious adverse events were similar in the rivaroxaban and enoxaparin comparator groups.

a) Bleeding:

Overall, the data show that, compared to enoxaparin, rivaroxaban increases the risk for bleeding. The only death due to bleeding occured among a patient who received rivaroxaban in the setting of concomitant non-steroidal drug intake.

The clinical database suggests that the absolute risk for bleeding is very small (< 1% of patients had major bleeding). Bleeding events were adjudicated for the RECORD studies by a committee blinded to treatment assignment. A prespecified charter described the types of information reviewed and the activities of the three-member committee. Specifically, any bleeding event was classified into two major categories:

- Major bleeding event
- Non-major bleeding event

Non-major bleeding events were further classified as to whether the events were clinically relevant or not, using specific criteria.

Table 5 summarizes the most important bleeding outcomes in the RECORD studies.

Table 5. Incidence Rates of Treatment-emergent Bleeding Events in the RECORD Studies

Endpoint	Riva n = 6183	Enox n = 6200	Absolute risk difference (95% CI)	Hazard ratio* (95% CI)	Nominal p-value
Major bleeding	24 (0.39%)	13 (0.21%)	0.18% (-0.01%, 0.37%)	1.8 (0.9, 3.6)	0.08
Major bleeding combined with surgical site bleeding	111 (1.80%)	85 (1.37%)	0.42% (-0.01%, 0.86%)	1.3 (1.0, 1.7)	0.06
Major or non-major clinically relevant bleeding	197 (3.19%)	158 (2.55%)	0.64% (0.05%, 1.23%)	1.3 (1.0, 1.5)	0.04
Any bleeding event	434 (7.02%)	401 (6.47%)	0.53% (-0.35%, 1.42%)	1.08 (1.0, 1.2)	0.3

*based on a Cox-regression analysis with study treatment as a covariate

b) Liver toxicity:

Overall, the clinical database provided an equivocal signal for liver toxicity. Of special note, the applicant presented summary data from the ATLAS TIMI 46 study to the advisory committee in order to support the contention that rivaroxaban lacked a signal for liver toxicity. These data were not part of the original NDA application and have not been reviewed by FDA. Also of note, is a recent report from the applicant that at least 20 subjects in the on-going atrial fibrillation studies have liver text abnormalities that meet the "Hy's law" signal for potential liver toxicity. The treatment assignment of these subjects is unknown. Hence, we anticipate a request for a blinded adjudication of these events.

A small imbalance between the two study groups was evident in the incidence of serious adverse events reported as due to increased alanine aminotransferase levels in the RECORD studies. In general, this imbalance was not evident in the comparison of the rates of other serious adverse events reported for liver test abnormalities, as shown in Table 6.

Table 6. Incidence Rates of Serious Adverse Events reported for Liver Test Abnormalities in the RECORD Studies

Event	Rivaroxaban n = 6183	Enoxaparin n = 6200
"Treatment-emergent" (during active treatment period and up to 2 days after last study drug dose)		
Alanine aminotransferase increased	17 (0.27%)	11 (0.18%)
Aspartate aminotransferase increased	5 (0.08%)	6 (0.10%)
Bilirubin increased	5 (0.08%)	4 (0.06%)
Alkaline phosphatase increased	0	1 (0.02%)
"Post-baseline" (at any time point during each study)		
Alanine aminotransferase increased	18 (0.29%)	14 (0.23%)
Aspartate aminotransferase increased	6 (0.10%)	8 (0.13%)
Bilirubin increased	5 (0.08%)	4 (0.06%)
Alkaline phosphatase increased	0	1 (0.02%)

The occurrence of blood ALT > 3X ULN concurrent with total bilirubin > 2X ULN has been proposed as potentially important indicator of drug-induced liver injury. Overall, within the pool of completed and ongoing studies (with available data) this outcome occurred in four rivaroxaban-treated patients who subsequently died with liver test abnormalities. The outcome (liver test abnormalities and death) occurred in two comparator group subjects.

9. Advisory Committee Meeting:

On March 19, 2009 the Cardiovascular and Renal Drugs Advisory Committee reviewed the rivaroxaban data. As previously noted, results from the recently completed ATLAS study were presented by the sponsor.

For the question of "Do the available clinical data demonstrate a favorable risk-benefit profile for rivaroxaban in the prophylaxis of VTE in patients undergoing hip or knee replacement surgery?" the Committee voted 15 (yes) to 2 (no). One member voted "no" due to concerns for potential for severe hepatotoxicity and the other had concerns for bleeding and overall benefits of rivaroxaban.

During discussion, committee members expressed varying levels of concern about the strength of the signals for hepatotoxicity and the feasibility of long term studies to further elucidate the hepatotoxicity seen with rivaroxaban. There were no objections from the committee members for approval without the data from the on-going "long term" atrial fibrillation studies. However, most members stated that longer term studies in identified populations are needed.

In regard to whether a lower dose than 10 mg should be available for special populations based PK/PD studies, the committee voted 5 (Yes) to 9 (No) (abstain 3). Many committee members expressed that there was not enough data to support a lower dose. While some

were persuaded that there might be a loss of efficacy others expressed concerns for safety in these specific patients.

10. Pediatrics:

The Pediatric Review Committee (PeRC) concurred with the applicant's request for a full waiver of PREA requirements because studies would be impossible or highly impracticable and because there are too few children with the disease/condition to study.

The applicant has met with the division to discuss a planned VTE treatment program (secondary VTE prevention) in pediatric patients.

11. Other Relevant Regulatory Issues:

The Office of Surveillance and Epidemiology has finalized a report that concludes information from the ongoing atrial fibrillation studies is essential to characterize the risks for potential severe liver toxicity. This observation is consistent with the primary clinical reviewer's contention and I agree.

During the review, the applicant expressed disagreement with FDA's perspective upon the "pooling" of the RECORD four studies and the applicant continues to maintain that this "pooling" is appropriate for inclusion in the proposed label. Label discussions were not held with the applicant during this review cycle.

In addition to the CMC deficiencies and the clinical requests to include in a Complete Review letter, the division is requesting information that provides verification of clinical data integrity. The Division of Scientific Investigations has identified important deficiencies based upon site inspection findings, as follows.

Division of Scientific Investigations (DSI): Though the application is submitted by Johnson & Johnson, the RECORD Studies were conducted by Bayer. To date, eight clinical sites have been inspected and only three sites had a determination of "no action indicated." The deficiencies at the five clinical sites range from failure to report serious adverse events to failure to maintain consistency with the protocol's randomization procedures. At one site, randomization was performed after surgery (not before, as the protocol specified). Additionally, inspection of Bayer monitoring procedures disclosed deficiencies in monitoring.

In other matters, the results of the establishment site inspection are pending. The proposed trade name (Xarelto) is regarded as reasonable (DMEPA findings). Additionally, a regulatory briefing for the Center management on May 1, 2009 supported the review team's decision to develop a Complete Review letter.

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/s/

Rafel Rieves

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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-406
Submission Code	000
Letter Date	22-Jul-2008
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Reviewer Name	Min Lu, M.D., M.P.H.
Review Completion Date	30-Mar-2009
Established Name	Rivaroxaban
(Proposed) Trade Name	XARELTO ™
Therapeutic Class	Anticoagulation
Applicant	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	10 mg once daily
Indication	Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE)
Intended Population	Patients undergoing hip or knee replacement surgeries.

Table of Contents

List of Abbreviations

AC/BE	Adjudication Committee/Bleeding Event
AC/CV	Adjudication Committee/Cardiovascular Event
AC/VTE	Adjudication Committee/Venous Thromboembolic Event
AE	adverse event
ALT	alanine aminotransferase
AP (ALKO PHOS)	alkaline phosphatase
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
bid	*bis in die*, twice daily
BMI	body mass index
BPM	beats per minute
BUN	blood urea nitrogen
CI	confidence interval
CK MB	creatine kinase muscle-brain
CYP	cytochromoe P450 isoforms
CT	computed tomography
CV	cardiovascular
DSMB	Data Safety and Monitoring Board
DVT	deep vein thrombosis
ECG	electrocardiogram
EMD	electromechanical dissociation
FiO2	fraction of inspired oxygen
FU	follow-up
FXa	Factor Xa
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GI	gastrointestinal
Hb	hemoglobin
Hct	hemotocrit
HIV	human immunodeficiency virus
ICAC	Independent Central Adjudication Committee
ICU	intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent to treat
IU	international unit
IV	intravenous(ly)
kg	kilogram
L	liter
LAP	Liver Advisory Panel
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
min	minute

MITT	Modified Intent to Treat (population)
mmHg	millimeter *hydrargyrum* (millimeter of mercury)
mmol	millimol
mL	milliliter
MRSA	methicillin-resistant staphylococcus aureus
ms	millisecond
MTD	maximum tolerance dose
N/A	not applicable
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
od	once daily
PE	pulmonary embolism
P-gp	P-glycoprotein
PO	*per os* (by mouth, orally)
PP	per protocol
prn	*pro re nata* (when daily doses for medication is variable)
PT	prothrombin time (in seconds)
RBC	red blood cell (count)
RECORD	**RE**gulation of **C**oagulation in **OR**thopedic Surgery to prevent
SC	subcutaneously
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SPA	Special Protocol Assessment
TB	total bilirubin
TEAE	treatment-emergent adverse event
THR	total hip replacement
TKR	total knee replacement
UH	unfractionated heparin
ULN	upper limit of normal
VKA	vitamin K antagonist
VTE	venous thromboembolic events
WBC	white blood cell (count)

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From clinical perspective, additional safety data of rivaroxaban from long-term studies including currently ongoing ROCKET-AF studies and recently completed trial of ATLAS ACS TIMI 46 6-months trial should be evaluated with regard to hepatotoxicity prior to approval of rivaroxaban for the currently proposed indication. The sponsor should be requested to submit the following information:

1) Report and results of an independent data safety monitoring board adjudication of the patients with liver markers (Hy's law case: ALT > 3X ULN with TB > 2X ULN) in the two ongoing ROCKET-AF studies. The adjudication should be conducted as blinded with pre-specified criteria and should include all cases up to date. These data should be unblinded to the Agency to determine whether or not there is an important imbalance in "Hy's law cases" in these two warfarin-controlled long-term studies.
2) Complete ATLAS ACS TIMI 46 study report with data sets.
3) A summary of the post-marketing experience, to include tabular and text summaries of spontaneously reported adverse events from other counties and an estimate of the numbers of patients exposed in the market place.
4) A summary of adverse events in the European post-marketing "observational study"

1.2 Risk Benefit Assessment

Xarelto (rivaroxaban) is a selective Factor Xa (FXa) inhibitor with oral bioavailability and is under development as an oral anticoagulant for the treatment of multiple thrombosis-mediated conditions. The currently proposed indication is for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgeries. The proposed dose of rivaroxaban is 10 mg once daily administered orally. The proposed treatment duration for rivaroxaban is 35 days for patients undergoing hip replacement surgery and 14 days for patients undergoing knee replacement surgery.

Efficacy Findings

Four multi-center, randomized controlled trials (RECORD 1-4) were conducted to support the currently proposed indication for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgeries. RECORD 1 and 2 studies were conducted in patients undergoing hip replacement surgery (THR) and RECORD 3 and 4 studies were in patients undergoing knee replacement surgery (TKR). In all 4 RECORD trials, rivaroxaban 10 mg once daily administered orally at least 6 to 8 hours after surgery was compared with enoxaparin administered subcutaneously. The enoxaparin dosing regimen was 40

mg once daily starting 12 hours preoperatively in RECORD 1-3 studies and was 30 mg twice daily starting 12 to 24 hours postoperatively in RECORD 4 study. The durations of active treatment for rivaroxaban and enoxaparin were similar in the RECORD studies with the exception of RECORD 2, in which treatment duration of Rivaroxaban was much longer than enoxaparin control (rivaroxaban 35 days versus enoxaparin 13 days). The dose regimen of enoxaparin (40 mg once daily) control in RECORD 3 study is not a recommended dose regimen of enoxaparin for the prophylaxis of DVT in patients undergoing TKR in the United States.

Altogether a total of 12,729 patients (6356 in the rivaroxaban group and 6373 in the enoxaparin group were randomized in 4 RECORD studies and 8,512 (67%) (4248 in the rivaroxaban group and 4264 in the enoxaparin group) were included in the Modified Intent to Treat (MITT) population for the primary efficacy analysis. About 30-39% of randomized patients in RECORD studies were excluded from MITT population mainly due to no adequate assessment of DVT. The primary efficacy endpoint was a composite endpoint of total VTE consisting of any DVT (proximal and/or distal), non-fatal PE, or death from all causes at the end of treatment in all 4 RECORD studies.

For patients undergoing THR surgery, the total VTE rate was 1.1% in the rivaroxaban group as compared to 3.7% in the enoxaparin group in RECORD 1 trial with similar treatment duration (35 days). In RECORD 2 study, the total VTE rate was 2.0% with rivaroxaban for 35 days as compared to 9.3% with enoxaparin for 13 days. The RECORD 1 study was designed as a non-inferiority trial and the result showed rivaroxaban to be non-inferior to enoxaparin (95% CI -3.55%, -1.51%) and superiority was further tested. There was a statistically significant difference in the total VTE rate between the two treatment groups in both studies ($p<0.001$).

For patients undergoing TKR surgery, the total VTE rate was 9.6% with rivaroxaban and 18.9% with enoxaparin 40 mg once daily, an unapproved regimen, in the RECORD 3 trial. In the RECORD 4 study, the total VTE was 6.9% with rivaroxaban and 10.1% with enoxaparin 30 mg twice daily. The RECORD 4 was designed as a non-inferiority trial and the result showed rivaroxaban to be non-inferior to enoxaparin (95% CI -5.25%, -0.17%) and superiority was further tested. There was a statistically significant difference in the total VTE rate between the two treatment groups in both studies ($p<0.05$).

For the secondary efficacy endpoints, major VTE rate (consisted of VTE-related death, non-fatal PE, or proximal DVT) was statistically significantly different ($p<0.05$) between the two treatment groups in RECORD 1 (0.2% and 2.0%, rivaroxaban and enoxaparin, respectively), RECORD 2 (0.6% and 5.1%, rivaroxaban 35 days and enoxaparin 13 day, respectively), and RECORD 3 (1.0% and 2.6%, rivaroxaban and enoxaparin 40mg, respectively) based on MITT population. In RECORD 4 study, the major VTE rate was not statistically significantly different between rivaroxaban and enoxaparin 30 mg bid regimen based on MITT population (1.2% and 2.0%, respectively).

Symptomatic VTE as one of the secondary efficacy endpoints was analyzed based on the safety population that included 12,383 (97%) subjects of randomized population. The symptomatic VTE rate was 0.27% in the rivaroxaban group as compared to 0.49% in the enoxaparin group in

RECORD 1 study. In RECORD 2 study, the symptomatic VTE rate was 0.08% with rivaroxaban and 0.33% with enoxaparin during the enoxaparin control period, and 0.16% with rivaroxaban and 0.90% with placebo during the placebo control period. In TKR trial, the symptomatic VTE was 0.66% with rivaroxaban and 1.94% with enoxaparin 40 mg once daily in RECORD 3, and 0.72% with rivaroxaban and 1.19% with enoxaparin 30 mg twice daily in RECORD 4 study. There was statistically significant difference in symptomatic VTE between the two treatment groups in RECORD 3 and in the placebo control period in RECORD 2 study only ($p<0.05$).

Overall, rivaroxaban demonstrates efficacy in prophylaxis of total VTE in patients undergoing elective hip or knee replacement surgeries. The absolute risk reduction of rivaroxaban for total VTE was 2.6% for total hip replacement surgery (RECORD 1 study), and 3.2% for total knee replacement surgery (RECORD 4 study) compared to currently available product (enoxaparin) with the similar treatment duration. The difference between the two treatments was mostly due to asymptomatic DVT. These results were based on 67% of all randomized population. There was no significant difference for the symptomatic VTE between the two treatments in these two studies based on 97% of randomized population.

Safety Findings

A total of 10,600 patients were exposed to rivaroxaban treatment in completed clinical studies including 6183 from phase 3 RECORD studies, 2232 from phase 2 VTE prophylaxis trials, 883 from phase 2 VTE treatment trials, 185 from phase 2 atrial fibrillation trials, and 1117 from phase 1 trials. Among all exposed patients, 6095 (57.5%) were exposed to rivaroxaban for ≤12 days, 3622 (34.2%) for 28-35 days, 203 (2%) between 36 and 12 weeks, and 635 (6%) for at least 12 weeks. There are 5 ongoing phase 3 trials including 4 long-term studies; 2 in patients with atrial fibrillation for prevention of stroke and 2 in patients with symptomatic VTE for prevention of recurrent VTE. The treatment duration is up to 4 years for atrial fibrillation and 3 to 12 months for VTE treatment. Currently, about 80% of planned patients have been enrolled in the atrial fibrillation trials as of the cutoff date of 5 December 2008 based on 6-month safety update.

In RECORD phase 3 studies, there were 13 (0.2%) and 25 (0.4%) deaths reported in the safety populations of rivaroxaban and enoxaparin, respectively, during the treatment and follow-up period. The serious treatment-emergent adverse event rate was 6.6% in the rivaroxaban group and 8.5% in the enoxaparin group. The serious adverse events that were reported more frequently with rivaroxaban compared to enoxaparin were ALT increased, wound infection, femur fracture, operative hemorrhage, wound secretion, anemia, post-operative wound infection, acute renal failure, device related infection, hemorrhage, and nausea. The overall percentage of adverse events that led to discontinuation was 3.7% in the rivaroxaban group and 4.7% in the enoxaparin group. The adverse events leading to permanent discontinuation that were higher with rivaroxaban compared to enoxaparin were hematuria, angina pectoris, upper abdominal pain, tachycardia, anesthetic complication, vomiting, peripheral edema, and acute myocardial infarction. Overall, 68% of rivaroxaban subjects and 69% of enoxaparin subjects reported at least one treatment-emergent adverse event. The common adverse events that were reported more

frequently on rivaroxaban compared to enoxaparin were peripheral edema, dizziness, pruritus, pain in extremity, urinary retention, muscle spasms, and wound secretion.

The following are main safety concerns for rivaroxaban based on the integrated review of safety data from the submission.

Bleeding events

The incidence of major bleeding was higher with rivaroxaban treatment (24, 0.39%) than with enoxaparin (13, 0.21%) in RECORD studies (p=0.07). There were two fatal bleeding events in the rivaroxaban group as compared to none in the enoxaparin group. Of the two subjects who experienced fatal bleeding events, one did not receive active treatment and another received rivaroxaban for 6 days and died of GI bleeding. Mjor bleeding events requiring re-operation occurred in 12 (0.19%) subjects in rivaroxaban group as compared to 7 (0.11%) subjects in the enoxaparin group. More patients experienced clinically overt extrasurgical site bleeding associated with a >2 g/dL decrease in hemoglobin or requiring blood transfusion >2 units in the rivaroxaban group (8, 0.13%) than in the enoxaparin group (1, 0.02%).

The incidence of major bleeding was relatively higher in the TKR patients (0.62% with rivaroxaban and 0.36% with enoxaparin) compared to the THR patients (0.20% with rivaroxaban and 0.09% with enoxaparin). The incidence of major bleeding was higher with rivaroxaban comparing with enoxaparin in all RECORD studies except RECORD 2 study (0.27% and 0.09% in RECORD 1, 0.08% and 0.08% in RECORD 2, 0.57% and 0.48% in RECORD 3, and 0.39% and 0.21% in RECORD 4 for rivaroxaban and enoxaparin, respectively).

In the RECORD studies, the incidence of clinically relevant non-major bleeding was also higher in the rivaroxaban group (177, 2.86%) than the enoxaparin group (145, 2.34%). The bleeding events reported more frequently in the rivaroxaban group than in the enoxaparin group were macroscopic hematuria (0.45% vs. 0.13%), rectal bleeding (0.32% vs. 0.1%), nose bleeding (>5 minutes) (0.13% vs. 0.06%), and vaginal bleeding (0.13% vs. 0.03%). Overall, the incidence of any bleeding was 7.0% in the rivaroxaban group as compared to 6.5% in the enoxaparin group.

In subgroup analyses, in Asian subjects, subjects with body weight ≤50 kg or >110 kg, or subjects with BMI<18.5 or ≥40, the risk of major or non-major clinically relevant bleeding events appear to be higher with rivaroxaban as compared to other groups.

Exploration of the data for potential drug-drug interactions suggested that patients on rivaroxaban with concomitant use of opioids and statins had 2.5 and 1.5-fold higher risk of major or clinical relevant non-major bleeding, respectively, as compared to those without use of these medications. The relative rate with use of opioids versus no use for major or non-major clinically relevant bleeding was nearly 2 fold on rivaroxaban (2.52) compared to enoxaparin (1.31). The relative rate with use of statin versus no use major or non-major clinically relevant bleeding was also higher on rivaroxaban (1.52) compared to enoxaparin (1.26). These potential drug-drug-interactions require further investigation.

Cardiovascular events

In RECORD 1 and 2 studies, retrospective adjudication was conducted for all deaths after the studies were unblinded. After retrospective adjudication, 5 more cardiovascular deaths and 1 more unexplained death were added in the enoxaparin control group and none was added in the rivaroxaban group. In the 4 RECORD studies, adjudicated cardiovascular events occurred in 31 (0.5%) subjects in the rivaroxaban group as compared to 39 (0.63%) subjects in the enoxaparin group during study drug treatment and the 30-day post-study drug follow-up period. There were more subjects with adjudicated ischemic stroke events in the rivaroxaban group (12, 0.19%) as compared to the enoxaparin group (7, 0.11%).

During the off-treatment period, 17 (0.28%) subjects experienced cardiovascular events in the rivaroxaban group as compared to 14 (0.23%) in the enoxaparin group. Among those patients, 11 (66%) events (4 MI, 3 stroke and 4 cardiovascular death) in the rivaroxaban group and 2 (14%) events (1 cardiovascular death and 1 unexplained death) in the enoxaparin group occurred within 10 days after the last dose of treatment; 7 (41%) events (2 MI, 2 stroke, and 3 CV deaths) in the rivaroxaban group and 1 (7%) events (CV death) in the enoxaparin group occurred within 5 days after the last dose of treatment.

There were more subjects who had ischemic stroke in the rivaroxaban group (6, 0.10%) than in the enoxaparin group (1, 0.02%) during the off treatment period. The 6 stroke events occurred in 4, 5, 8, 13, 34, and 39 days after the last dose of treatment in 6 subjects, respectively. One stroke event in the enoxaparin group occurred 26 days after the last dose of treatment.

The early occurrence of cardiovascular events and a higher incidence of ischemic stroke during off-treatment period in the rivaroxaban group as compared to the enoxaparin group raise concerns for possible rebound effect of rivaroxaban after treatment withdrawal.

Hepatic events

In the Phase 3 RECORD studies, laboratory evaluation showed that the elevation of ALT>3xULN was observed in 152 (2.5%) subjects in the rivaroxaban group as compared to 227 (3.7%) subjects in the enoxaparin group. There were 9 (0.15%) patients who had ALT >3xULN concurrent with TB >2xULN in the rivaroxaban group as compared to 7 (0.11%) patients in the enoxaparin group. The events of ALT >3xULN concurrent with TB >2xULN in 7 (0.11%) subjects in the rivaroxaban group as compared to 3 (0.05%) subjects in the enoxaparin group were considered to be possible related to the study drug by at least one member of the sponsor's liver advisory panel.

In the RECORD studies, 290 subjects (4.7%) in the rivaroxaban group and 400 subjects (6.5%) in the enoxaparin group reported a post-baseline hepatic disorder adverse event. The vast majority of these adverse events reported by investigators in both treatment groups were adverse events due to abnormal liver-related laboratory tests. Of these, the most frequently reported events included the following: increased ALT (144 [2.3%] with rivaroxaban and 200 [3.2%] with enoxaparin); increased AST (116 [1.9%] with rivaroxaban and 152 [2.5%] with enoxaparin); and

increased GGT (126 [2.0%] with rivaroxaban and 183 [3.0%] with enoxaparin). Overall, 33 subjects (0.53%) administered rivaroxaban and 27 subjects (0.44%) administered enoxaparin had hepatic disorder serious adverse events**.** The vast majority of these subjects (28 subjects [0.5%] receiving rivaroxaban and 26 subjects [0.4%] receiving enoxaparin) had adverse events that were increases in liver-related laboratory parameters. The most common hepatic disorder serious adverse event was increased ALT levels, seen in 17 subjects (0.3%) in the rivaroxaban group and 14 subjects (0.2%) in the enoxaparin group.

In Phase 2 VTE prophylaxis trials (8 days), 4 subjects in the rivaroxaban group and 2 subjects in the enoxaparin group had ALT >3xULN concurrent with TB >2xULN. The events in all 4 subjects in the rivaroxaban group were considered by the investigator to be related to the study treatment and the events in 2 subjects in the enoxaparin group were considered by the investigator to be not related to the study drug. One subject in the rivaroxaban group was hospitalized with clinical symptoms, increased liver enzymes, bilirubin, alkaline phosphate, and GGT 39 days after the last dose of rivaroxaban and subsequently died of "septic, cholemic heart and circulatory failure with bronchial pneumonia, acute cholecystitis and acute pancrititis" per autopsy. Autopsy performed 3 days after the death showed "hepatocytes already altered due to autolysis, portal fields not greatly enlarged, no glycogen nuclei, no signs of intrahepatic cholestasis". The investigator considered the liver impairment and pancrititis as related to the study drug. The liver advisory panel concluded that this may be a drug-induced cholestasis but it was unlikely to be related to rivaroxaban although temporal association cannot exclude rivaroxaban.

In Phase 2 VTE treatment trials (12 week), one subject in the rivaroxaban group had ALT >3xULN concurrent with TB >2xULN as compared to none in the heparin/VKA control group. This subject died of liver failure after 48 days of treatment with rivaroxaban 40 mg once daily. This subject was diagnosed with acute hepatitis B infection by positive HBcAb IgM. The patient had HBsAg positive at baseline identified by retention blood sample. The autopsy showed liver tissue with subacute necrosis without acute inflammatory changes and suggested the presence of acute exacerbation of chronic hepatitis B and of probably toxic origin. The pathologist in the liver advisory panel concluded that the submassive necrosis of liver can be explained by severe hepatitis B viral infection taking into account the serological profile of hepatitis B but such lesion might also be consistent with drug-induced or toxic damage to the liver.

In a Phase 2 Japanese atrial fibrillation trial (28 days) in 102 subjects, ALT>1x ULN was reported in 13% in the rivaroxaban group (75 subjects) as compared to 4% in the warfarin group (27 subjects), although the sample size was relatively small.

In 5 ongoing studies (2 open-label and 3 blinded), a total of 27 subjects have been reported as having ALT >3xULN concurrent with TB >2xULN. In two open-labeled studies, these included 3 subjects in phase 2 ATLAS ACS TIMI 46 study (all 3 in placebo group), 3 subjects in EINSTEIN DVT/PE study (all 3 in rivaroxaban group) who had ALT >3xULN concurrent with TB >2xULN. One subject in placebo group in ATLAS ACS TIMI 46 study and 2 subjects in the rivaroxaban group in EINSTEIN DVT/PE subsequently died. One subject in the rivaroxaban group died with liver failure and the liver advisory panel member raised concerns of likely drug-

induced toxic injury based on autopsy findings. In the 3 blinded ongoing studies, there were 16 cases in ROCKET-AF study, 3 in J-ROCKET-AF study, and 2 in MAGELLaN study. Three cases in ROCKET-AF were unblinded and all had received warfarin. One case in J-ROCKET-AF study was unblinded and had received rivaroxaban. One case in MAGELLaN study was unblinded and had received enoxaparin. A total of 16 cases are still blinded.

Overall, in completed studies, there were 14 (0.15%) subjects who had ALT >3xULN concurrent with TB >2xULN in the rivaroxaban group as compared to 9 (0.13%) in the control group. In RECORD phase 3 trials, 7 (0.11%) in the rivaroxaban group and 3 (0.05%) in the enoxaparin group were considered to be possibly related to rivaroxaban by at least one member of the sponsor's liver advisory panel. Two of 14 subjects in the rivaroxaban group subsequently died with liver failure as compared to none in the enoxaparin group. One death was considered to be drug-induced cholestasis by the liver advisory panel. Another death was considered to be hepatitis B infection but the autopsy findings of liver tissues raised concerns for possible toxic origin of lesions. In both cases, the role of rivaroxaban could not be excluded. An additional 27 cases of ALT >3xULN concurrent with the TB >2xULN were reported in 5 ongoing studies. These included 4 in the rivaroxaban group, 3 in the placebo group, 3 in the warfarin group, 1 in the enoxaparin group and 16 still blinded cases. One subject in the rivaroxaban group in ongoing studies died with liver failure and the autopsy findings again raised concerns of likely drug-induced toxic injury to a liver advisory panel member.

In the RECORD studies, serious treatment-emergent ALT increased was reported more often in subjects in the rivaroxaban group (17, 0.27%) as compared to enoxaparin group (11, 0.18%) although the rate of ALT>3x ULN was lower with rivaroxaban (152, 2.48%) than with enoxaparin (227, 3.70%). Because enoxaparin control has been known to cause benign liver enzyme elevation and such elevations are fully reversible (NDA 20-164, Lovenox labeling), the comparison of liver enzyme elevation between the two treatments would not eliminate the concerns of possible serious liver toxicity for rivaroxaban.

Previous experience with EXANTA (ximelagatran) that causes drug-induced liver injury suggested even short term tolerance does not necessarily predict long term safety (NDA 21-686, Medical Review, Dr. Ruyi He, M.D., 9/27/04; Cardiovascular and Renal Drug Advisory Committee Transcript, 9/10/04). In the current application, 92% of study patients were exposed to <35 days of rivaroxaban treatment and only 6% (635 patients) were exposed to rivaroxaban for 3 months based on completed studies. Therefore, the long-term safety data from ongoing studies, using a control that has not been shown to increase liver enzymes, such as warfarin, will be needed to fully evaluate the hepatotoxicity for rivaroxaban.

Furthermore, because rivaroxaban is an oral anticoagulant that doesn't require routine monitoring during treatment, off-label, long-term use could be widespread in clinical practice to replace current available oral product (coumadin) due to convenience, especially in atrial fibrillation population for stroke prevention and in patients who require long-term VTE prophylaxis and treatment. The prevalence of atrial fibrillation in the United States has been projected to increase from 2 to 5 million in 2000 to 6 to 12 million in 2050 (Special Report,

Prevention of Atrial Fibrillation, Report from a National Heart, Lung, and Blood Institute Workshop, *Circulation* 2009; 119:606-618). Therefore, thorough evaluation for hepatotoxicity and long-term safety in the long-term clinical trial is extremely important.

Creatinine and urea abnormalities

In RECORD studies, the incidence of treatment-emergent creatinine and urea abnormalities >1x ULN was higher in the rivaroxaban group as compared to enoxaparin group in THR trials (10.3% and 8.0% for creatinine, and 9.2% and 7.5% for urea, in rivaroxaban and enoxaparin respectively) as well as TKR trials (12.9% and 11.6% for creatinine, and 9.6% and 7.8% for urea, in rivaroxaban and enoxaparin respectively). There were slightly more reported serious treatment-emergent renal and urinary disorders [13 (0.21%) and 10 (0.16%)] and any treatment-emergent renal and urinary disorders [(5.39%) and 309 (4.98%)] in the rivaroxaban group than in the enoxaparin group. More urinary retention, hematuria, serious acute renal failure, and renal impairment events were reported in the rivaroxaban group than in the enoxaparin group. These raise concerns of possible renal toxicity for rivaroxaban and will require further investigation.

In summary, rivaroxaban increased absolute risk of major bleeding by 0.2% as compared to currently available product (enoxaparin) in patients undergoing THR or TKR surgeries. Rivaroxaban has been associated with fatal bleeding, required more re-operation and blood transfusions in phase 3 trials. In addition, rivaroxaban increased absolute risk of clinical relevant non-major bleeding by 0.5% comparing to current available therapy. It was associated with more macroscopic hematuria, rectal bleeding, nose bleeding >5 minutes, and vaginal bleeding.

There were more ischemic stroke and earlier occurrence of cardiovascular events during the off-treatment period with rivaroxaban than with enoxaparin. This raises concerns of possible rebound effect of rivaroxaban after the treatment withdrawal.

There were more possible related ALT >3x ULN concurrent with total bilirubin >2x ULN, more reported serious ALT increased with rivaroxaban than with enoxaparin in phase 3 trials. In addition, 2 subjects with ALT >3x ULN concurrent with total bilirubin >2x ULN subsequently died with liver failure in the rivaroxaban group as compared no liver-related deaths in the enoxaparin group in the completed studies, and additional one death with liver failure in ongoing study raise concerns of possible liver toxicity for rivaroxaban. Long-term safety data will be needed to fully evaluate the hepatotoxicity for rivaroxaban. Several long-term studies are ongoing and they should provide sufficient data for evaluation.

There was a higher incidence of creatinine and urea elevations with rivaroxaban than with enoxaparin in phase 3 trials. This raises concerns of possible renal toxicity and will require further investigation.

Benefits/Risks

Three products are currently available on the market for the proposed indication for the prophylaxis of DVT. In the RECORD studies, Rivaroxaban was shown to be superior to the comparator enoxaparin mainly for venographically detected asymptomatic DVT. However, rivaroxaban was not shown superior to enoxaparin for clinically important outcomes, such as pulmonary embolism. Rivaroxaban has shown an increased risk for major bleeding as compared to enoxaparin in these studies. Additional safety data of rivaroxaban from ongoing ROCKET-AF studies and recently completed trial of ATLAS ACS TIMI 46 6-months trial should be submitted for evaluation of the risk for hepatotoxicity to allow assessment of benefit and risk of rivaroxaban for the proposed indication.

1.3 Recommendations for Postmarketing Risk Management Activities

N/A

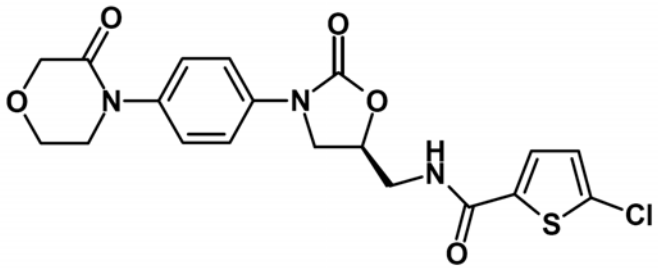
1.4 Recommendations for other Post Marketing Study Commitments

N/A

2 Introduction and Regulatory Background

2.1 Product Information

Rivaroxaban is a selective Factor Xa inhibitor with oral bioavailability. The chemical name of rivaroxaban is: 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide. The structural formula is:



The molecular formula of rivaroxaban is $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89. Rivaroxaban is a pure (*S*)-enantiomer. It is an odorless, non-hygroscopic, white to yellowish powder.

Drug established name: Rivaroxaban (BAY 59-7939) (JNJ-39039039)

Proposed trade name: Xarelto

Pharmaceutical class: Anti-Factor Xa products

Proposed indication: The proposed indication is for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing:

- hip replacement surgery
- knee replacement surgery.

Proposed Dosage Form, Route of Administration, and Dosing Regimen:

The drug product proposed for marketing is a rivaroxaban 10 mg film coated oral tablet. The tablets are round, light red biconvex film-coated marked with a triangle pointing down above a "10" on one side, and an "Xa" on the other side.

The proposed dose of rivaroxaban is 10 mg taken orally once daily.

The proposed treatment duration is 35 days for patients undergoing hip replacement surgery and 14 days for patients undergoing knee replacement surgery.

2.2 Tables of Currently Available Treatments for Proposed Indications

The currently approved available products for the proposed indications, including populations, main safety concerns, dosage and administrations are shown in the table below.

Currently approved anticoagulants for prophylaxis of DVT or PE in patients undergoing hip or knee surgeries in US

Indications	Approved Products	Populations	Safety	Dosage And administration
Prophylaxis of DVT in patients undergoing hip replacement surgery	Lovenox (enoxaparin sodium)	Adults	Boxed WARNING for Spinal/epidural hematoma	30 mg q12 hrs beginning post-operatively; continue for 7-10 days, up to 14 days; 40 mg q.d. beginning pre-operatively for 7-10 days; may continue for 3 weeks; SC
	Fragmin (dalteparin sodium)	Adults		5000 IU q.d.; may beginning pre-operatively; continue for 5-10 days, up to 14 days; SC
	Arixtra (Fondaparinux sodium)	Adults		2.5 mg administered by subcutaneous injection once daily beginning 6 to 8 hours post-operatively; continuing for 5-9 days
Prophylaxis of DVT in patients undergoing knee replacement surgery	Lovenox (enoxaparin sodium)	Adults		30 mg q12 hrs beginning post-operatively; continuing for 7-10 days, up to 14 days; SC
	Arixtra (Fondaparinux sodium)	Adults		2.5 mg administered by subcutaneous injection once daily beginning 6 to 8 hours post-operatively; continuing for 5-9 days
Prophylaxis of DVT (Non-specific patient population)	Heparin Sodium (unfractionated heparin)	Adults and Pediatrics	WARNINGS for Hemorrhage, Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia Thrombosis (HITT)	5000 U t.i.d or b.i.d beginning pre-operatively; continuing for 7 days; SC
	Argatroban	Adults and Pediatrics with heparin-induced thrombocytopenia.	WARNINGS for Hemorrhage	Initial dose of 2 mcg/kg/min, administered as a continuous infusion
	Coumadin (warfarin Sodium)	Adults	WARNINGS for bleeding risk	Individualized to INR of 2.0-3.0; Oral

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

This product has not been approved in the U.S. No product containing rivaroxaban is approved in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

Anticoagulants have been associated with risk of hemorrhage. Low molecular weight heparins (Lovenox and Fragmin) and Arixtra have a black boxed warning for spinal or epidural hematomas when neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed. Heparin and low molecular weight heparins have warnings for heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia thrombosis (HITT).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Initial IND (64,892) for Rivaroxaban (BAY 59-7939) for prophylaxis of VTE was submitted on May 29, 2002 by Bayer HealthCare Pharmaceuticals. Two End of Phase 2 meetings were held on July 5, 2005 and November 18, 2005 to discuss the phase 3 clinical programs. All clinical studies including phase 3 studies were conducted under the INDs. Four phase 3 efficacy and safety studies were submitted in December 2005 for special protocol review and subsequently the four protocols were revised as requested by the Division. The Division agreed that the revised study design and planned analysis of studies adequately address the objectives necessary to support a regulatory submission. A Pre-NDA meeting was held between the sponsor and the Agency on (July 20, 2007) to discuss the adequacy of the completed clinical, pre-clinical and chemistry, manufacturing and controls data for submitting a NDA and NDA format.

2.6 Other Relevant Background Information

N/A

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission of this NDA is in eCTD format. There were 17 amendments to the original submission.

The following material in the NDA submission was reviewed:

- NDA 22-406 No. 0000, eCTD format, submitted July 28, 2008
- Amendment No. 0001, General correspondence, submitted on August 11, 2008
- Amendment No. 0003, General correspondence (response to questions), submitted on November 4, 2008
- Amendment No. 0007, 4-month safety update for ongoing clinical studies, submitted on November 25, 2008
- Amendment No. 0009, Response to information request, submitted on December 18, 2008
- Amendment No. 0011, Response to information request, submitted on December 24, 2008

- Amendment No. 0012, Response to information request, submitted on January 6, 2009
- Amendment No. 0013, Response to information request, submitted on January 13, 2009
- Amendment No. 0015, Response to information request, submitted on January 23, 2009
- Amendment No. 0016, Response to information request, submitted on January 23, 2009
- Amendment No. 0020, 6-month Safety Update, submitted on February 2, 2009

Two sites (14029 and 32006) under two different investigators in RECORD 4 study were identified having significant issues in conducting clinical trials. One site (14029) was excluded and another site (32006) was included in the data analysis by the sponsor.

Inspection by the FDA field investigators was requested for eight study sites that showed strong efficacy (two in each of the 4 pivotal studies). The inspection results are currently pending.

3.2 Compliance with Good Clinical Practices

Informed consent was required from patients in all clinical trials. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

3.3 Financial Disclosures

The sponsor certified that there was no financial arrangement with clinical investigators who conducted the clinical studies (Form FDA 3454).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Pending.

4.2 Clinical Microbiology

Pending.

4.3 Preclinical Pharmacology/Toxicology

In a 13-week repeat-dose toxicity study in mice at oral gavage doses of 50, 100 and 200 mg/kg/day (PEG-6000 co-precipitate), higher incidences of fibrosis of the heart, mononuclear cell infiltration in kidneys, hyperplastic spindle cells in adrenal, increased cellularity of marginal zones of the spleen in males, and high incidences of Kupffer cell foci in the liver of high dose

group indicated the liver and kidneys as being the target organs of toxicity in both sexes, and additional targets of toxicity in males were adrenal and spleen. A 100 mg/kg/day dose was MTD in the study. The plasma exposure was 20 and 29.5 times the exposure produced by the clinical dose in man.

In another 13-week toxicity study, CD-1 mice were fed 1250, 2500 and 5000 ppm of compound in dietary admixture (10% PEG-6000 coprecipitate) and mean drug administered was 237, 476 and 1007 mg/kg/day. A dose dependent increase in coagulation time and, increased liver enzymes activities and incidences of focal renal tubular hypertrophy in males in the highest dose group, and focal necrosis of liver in females in the middle and the highest dose groups was noted. The kidney and liver were the target organs of toxicity in males and females and 5000 ppm in diet appears to be the MTD. The exposure levels ($AUC_{0\text{-}24h}$) at study MTD (high doses) were 31.3 and 43.0 mg.h/L in males and females, i.e., about 7 and 10 times the human exposures at the clinical dose of 60 mg/day (30 mg b.i.d).

In a 4-week oral gavage toxicity study in rats conducted at doses of 0, 12.5, 50 and 200 mg/kg/day, 12% decrease in body weight of high dose males and, treatment related increase in several liver enzyme activities in treated animals. High incidences of bilateral retinal atrophy, focal inflammation of the pancreas and unilateral diffuse tubular dilatation of the testes were suggestive of eyes, pancreas and testes as the target organs of toxicity. A dose between 50 and 200 mg/kg/day was the highest tolerable dose and it provides 68 to 162 multiples of human plasma concentration.

In a 13-week oral gavage toxicity study in rats, oral doses of 12.5, 50 and 200 mg/kg/day produced treatment related increase in ALT in high dose treatment group.

The another 13-week oral gavage toxicity study in rats, at oral doses of 12.5, 50 and 200 mg/kg/day and an increased ALT levels (23%) were seen in high dose group animals and these were not completely reversed in recovery group. The incidences of pigment deposition in the pancreas, mesenteric lymph node hemorrhage and focal retinal atrophy in the eye were seen in males and the increased incidences of epicarditis, congestion of lungs, thymic and mesenteric lymph node hemorrhage were seen in females. The high dose (200 mg/kg/day) appeared to be the MTD in this study.

In the 26-week study in rats using administration by gavage, an increase of ALT was seen at the interim clinical-pathological investigation. In all studies, the effect was transient and vanished despite continuation of treatment.

In the 26-week study in rats, birefringent crystals were seen in the urine at 50 mg/kg and above which were shown to consist of rivaroxaban in a separate mechanistic study. It is assumed that rivaroxaban concentrations in the highly concentrated rat urine exceed the maximum rivaroxaban solubility resulting in precipitation of unchanged drug. Morphological investigation of the kidneys and the lower urinary tract, did not reveal any irritative effects deriving thereof.

Pharmacology/Toxicology review is pending.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Rivaroxaban inhibits Factor Xa in the coagulation cascade that would therefore be hypothesized to inhibit coagulation and thrombus formation.

4.4.2 Pharmacodynamics

Dose-dependent inhibition of FXa activity was observed in humans and the prothrombin time, activated partial thromboplastin time and HepTest® are prolonged dose-dependently. The relationship between prothrombin time and rivaroxaban plasma concentration is linear and closely correlated. In accordance with the pharmacokinetics, prolongation of the prothrombin time using the Neoplastin® assay reached half of the maximum effect within 0.5-1 hours and maximum effect within 2-4 hours after administration of a tablet. The offset of pharmacodynamic effect also closely parallels the pharmacokinetic half-life.

Clinical pharmacology review is pending.

4.4.3 Pharmacokinetics

Rivaroxaban was readily absorbed after oral administration of the immediate-release tablet, with peak plasma concentrations approximately 2 to 4 hours after dosing. Rivaroxaban is highly bound to plasma proteins at approximately 92% to 95%, with serum albumin being the main binding component. Due to its high plasma protein binding rivaroxaban is not expected to be dialyzable.

Excretion of rivaroxaban and metabolites occurred via both renal and fecal routes. Of the administered rivaroxaban dose, approximately two thirds underwent metabolic degradation, with half eliminated renally and the other half eliminated by the fecal route. The final one third of the administered dose underwent direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Major metabolic pathways include oxidative degradation (hydroxylation followed by ring cleavage) and hydrolysis (with subsequent conjugation). In addition to unchanged rivaroxaban, one main metabolite, which does not possess any anticoagulant activity, was identified in excreta. Unchanged rivaroxaban was the most important compound in human plasma with no major or active circulating metabolites being present. Cytochrome P-450 (CYP) 3A4/3A5 accounts for approximately 18% and CYP2J2 for approximately 14% of total rivaroxaban elimination, respectively. The terminal half-live of rivaroxaban is approximately 5 – 9 hours in young male healthy subjects, and 11-13 hours in the healthy elderly.

Seventeen drug-drug interaction studies were conducted. The results of those studies showed that strong inhibitors of both metabolism (i.e., CYP3A4) and active secretion (i.e., P-glycoprotein [P-

gp] and breast cancer resistance protein [Bcrp]) may result in a clinically relevant increased systemic exposure of rivaroxaban.

In healthy elderly subjects (65-80 years of age) higher mean AUC values by 52% in males and by 39% in females were observed when compared to young subjects of the same sex. This was accompanied by an increase in C_{max} by 35% in both sexes and by terminal half-lives between 11 and 13 h. The study in subjects older than 75 years confirmed these results, showing approximately 41% higher AUC values in comparison to young subjects, which was mainly due to reduced (apparent) total body clearance and renal clearance. No relevant age effects could be observed for C_{max} (8% increase in elderly) or time to reach the maximum plasma concentration (t_{max}).

In subjects with mild (creatinine clearance 50 to <80 mL/min), moderate (creatinine clearance 30 to <50 mL/min) or severe renal impairment (creatinine clearance 15 to <30 mL/min) rivaroxaban plasma exposure (C_{max} and AUC) were increased and the overall inhibition of FXa activity was increased by 1.5-, 1.9- and 2.0-fold respectively, compared with healthy subjects with normal renal function (creatinine clearance >80 mL/min). In addition, the increased overall plasma concentrations were associated with an increased sensitivity of prothrombin time prolongation. No clinical data are available for patients with kidney failure (creatinine clearance <15mL/min).

Cirrhotic subjects with mild liver impairment (Child-Pugh Grade A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase for AUC on average) and pharmacodynamics, which were comparable to their matched healthy control group. In cirrhotic subjects with moderate hepatic impairment (Child-Pugh Grade B- all with baseline prothrombin time prolongations), rivaroxaban plasma concentrations were significantly increased (2.3 fold for AUC on average) as were the pharmacodynamic effects compared to subjects with normal hepatic function. Cirrhotic subjects with severe hepatic impairment (Child Pugh Grade C) were not studied.

Clinical pharmacology review is pending.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The following tables list the completed and ongoing studies in the rivaroxaban development program. All completed studies were short-term studies. Among those studies over 10,000 patients were exposed to rivaroxaban treatment. These included 4 RECORD phase 3 studies in patients undergoing hip or knee replacement surgeries, 9 phase 2 studies, and about 50 phase 1 studies.

Among the ongoing studies, 4 are long-term phase 3 studies including 2 in patients with atrial fibrillation for prevention of stroke and 2 in patients with symptomatic VTE for prevention of recurrent VTE. These 4 studies planned to enroll about 22,000 patients.

Completed Clinical Studies

Study Details Phase / Study Number	Rivaroxaban Dose	Control Group	Safety Pop/ RIVA Subjects in Safety Pop (any dose)[a] (N)	Scheduled duration of treatment
Phase 3: VTE Prevention				
RECORD 1 (11354)	10 mg od	Enox 40 od	4433/2209	35,36±4 days[l]
RECORD 2 (11357)	10 mg od	Enox 40 od	2457/1228	35±4,13±24 days[b]
RECORD 3 (11356)	10 mg od	Enox 40 od	2459/1220	12,13±2 days[l]
RECORD 4 (11355)	10 mg od	Enox 30 bid	3034/1526	12±2 days
Total			**12,383/6,183**	
Phase 2: VTE Prevention				
10942	2.5, 5, 10, 20, and 30 mg bid; 30 mg od	Enox 40 od	625/463	8, 9±2 days[b]
10944	2.5, 5, 10, 20, and 30 mg bid	Enox 40 od	704/572[c]	8, 9±2 days[b]
10945	2.5, 5, 10, 20, and 30 mg bid	Enox 30 bid	613/509	8±2 days
11527	5, 10, 20, 30, and 40 mg od	Enox 40 od	845/688[d]	8, 9±2 days[b]
Total			**2787/2232**	
Phase 2: VTE Treatment				
11223	10, 20 and 30 mg bid; 40 mg od	Enox/VKA	604/478	12 weeks
11528	20, 30, and 40 mg od	Heparin/VKA	542/405	12 weeks
Total			**1146/883**	
Phase 2: Atrial Fibrillation (Japan)				
11390	10, 20 and 30 mg bid	NA	36/36	28 days
11866	10, 15 and 20 mg od	Warfarin	102/75	28 days
12024	2.5, 5 and 10 mg bid	Warfarin	100/74	28 days
Total			**238/185**	
Phase 1: Clinical Pharmacology				
51 Studies	Variable[e]	Variable[e]	1298/1117	≤10 days[e]
Grand Total			**17,852/10,600**	

[a] Summarizes the total number of subjects exposed to any dose of study drug (active or dummy).
[b] The first number refers to the duration on rivaroxaban, and the second number refers to the duration on enoxaparin.
[c] One additional subject received study drug but had no safety assessments; subject not included in the safety analyses
[d] Seven subjects received study drug but had no safety assessments; subjects not included in the safety analyses (Figure 11-1, Study 11527 [MRR-00174])
[e] The majority of Phase 1 clinical pharmacology studies were uncontrolled or of a crossover design. Fifteen of 51 studies used a concurrent placebo group. More than 80% of subjects exposed to rivaroxaban received study drug for 1 day only.

Key: RIVA = rivaroxaban; od = once daily; bid = twice a day; Enox = Enoxaparin ; Enox/VKA = Enoxaparin followed by vitamin K antagonist; Heparin/VKA = heparin treatment followed by vitamin K antagonist; NA = not applicable; VTE = venous thromboembolism; Pop=population

Table 1: Overview of Ongoing Clinical Studies in Patients

Study Details Phase / Study Number	Rivaroxaban Total Daily Dose(s)	Comparator	All Subjects in Safety Population (N/total planned enrollment)	Scheduled Treatment duration
Phase 3:				
EINSTEIN DVT/PE[a] (11702)	30 mg for 3 weeks; then 20 mg	Enoxaparin/ VKA	3358/6200+	3, 6 or 12 months
EINSTEIN Extension (11899)	20 mg	Placebo	840/1300+	6 or 12 months
ROCKET-AF (11630)	20 mg 15 mg[b]	Warfarin	11018/14000+	Chronic (up to 4 years)
J-ROCKET-AF (12620) Japan	15 mg 10 mg[c]	Warfarin	1184/1200*	Chronic (up to 2.5 years)
MAGELLaN (12839)	10 mg	Enoxaparin/ Placebo	987/~8000+	35 days
ATLAS ACS 2 TIMI 51 (13194)	5 and 10 mg	Placebo	5/13500+	Chronic (up to 2.5 years)
Phase 2				
ATLAS ACS TIMI 46 (11898)	5, 10, 15 and 20 mg	Placebo	3462/3500+	6 months
Phase 1				
CHF (12980)	10 mg	Placebo or Enoxaparin	21/36+	6 days
Grand Total			20,875/47,736	

Key: CHF = congestive heart failure.
[a] For the purpose of this ISS, the 2 studies (EINSTEIN-DVT and EINSTEIN-PE) are presented together.
[b] In ROCKET-AF, subjects with moderate renal impairment on entry to the study received 15 mg rivaroxaban.
[c] In J-ROCKET-AF, subjects with moderate renal impairment on entry to the study received 10 mg rivaroxaban.
Note: Safety data from these 9 ongoing studies are presented as of last subject visit cutoff date of either 31 October 2008 or 5 December 2008.
Source: Study 11898, Table 1.1; Study 11702, Table 1; Study 11899, Table 1; Study 11630, Table 1.1.1; Study 12620, Table 1.1.1; Study 12839, Table 1, and Study 12980, Table 1.
+ As of cutoff date of 5 December 2008. For ATLAS ACS TIMI 46, the database was locked 18 October 2008.
* As of cutoff date of 31 October 2008.

5.2 Review Strategy

Four RECORD phase 3 studies were reviewed for efficacy for the proposed indications. These four trials were reviewed separately in the same depth. These four trials and other completed and ongoing trials were reviewed for safety.

5.3 Discussion of Individual Studies

RECORD Studies

Four RECORD studies (RECORD 1, 2, 3 and 4) were conducted to support the proposed indication for Rivaroxaban. All 4 trials were randomized, double-blind, double-dummy, active-controlled studies that evaluated the efficacy and safety of oral rivaroxaban. RECORD 1 and 2 studies were in patients undergoing hip replacement surgery (THR) and RECORD 3 and studies were in patients undergoing knee replacement surgery (TKR).

In all 4 RECORD trials, Rivaroxaban was administered at a dose of 10 mg once daily at least 6 to 8 hours after surgery (wound closure) for the prevention of DVT and PE after elective THR or TKR surgery.

Subcutaneous enoxaparin was chosen as the active comparator in all 4 RECORD studies. The enoxaparin dosing regimen in RECORD 1 (11354), RECORD 2 (11357) and RECORD 3 (11356) was 40 mg once daily starting 12 hours preoperatively. The enoxaparin regimen in RECORD 4 (11355) was 30 mg twice daily starting 12 to 24 hours postoperatively. It should be noted that the enoxaparin dose regimen (40 mg once daily) in RECORD 3 study is not an approved dose regimen of enoxaparin for the prophylaxis of DVT in patients undergoing TKR surgery in United States.

The durations of active treatment for rivaroxaban and enoxaparin were similar in each of the RECORD studies with the exception of RECORD 2, in which treatment duration of Rivaroxaban was much longer than enoxaparin control (35 days rivaroxaban versus 13 days enoxaparin).

The following table shows the study design, treatment and duration, number of patients in each of the RECORD trials.

Study design, dose regimen and treatment duration in RECORD studies

Study Identifier, Location of Study Reports, Study Dates (FPV-LPV)*	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Total and Per Dose (Safety Population)	Population	Scheduled Duration of ActiveTreatment	Top 3 Enrolling Countries
RECORD 1 11354 (MRR-00233) February 2006 to March 2007	Randomized, double-blind, double-dummy, active control	Rivaroxaban oral: 10 mg od Enoxaparin SC: 40 mg od	4433 treated 2209 2224	Total hip replacement	Rivaroxaban 10 mg od: 35 ± 4 days Enoxaparin 40 mg od: 36 ± 4 days	Poland Germany Austria
RECORD 2 11357 (MRR-00234) February 2006 to June 2007	Randomized, double-blind, double-dummy, active control	Rivaroxaban oral: 10 mg od Enoxaparin SC: 40 mg od	2457 treated 1228 1229	Total hip replacement	Rivaroxaban 10 mg od: 35 ± 4 days Enoxaparin 40 mg od: 13 ± 2 days	China Sweden United Kingdom
RECORD 3 11356 (MRR-00218) February 2006 to January 2007	Randomized, double-blind, double-dummy, active control	Rivaroxaban oral: 10 mg od Enoxaparin SC: 40 mg od	2459 treated 1220 1239	Total knee replacement	Rivaroxaban 10 mg od: 12 ± 2 days Enoxaparin 40 mg od: 13 ± 2 days	Spain Poland Germany
RECORD 4 11355 (MRR-A41857) June 2006 to January 2008	Randomized, double-blind, double-dummy, active control	Rivaroxaban oral: 10 mg od Enoxaparin SC: 30 mg bid	3034 treated 1526 1508	Total knee replacement	Rivaroxaban 10 mg od: 12 ± 2 days Enoxaparin 30 mg bid: 12 ± 2 days	United States India Canada

*FPV = First patient visit; LPV = Last patient visit.
Active treatment = pharmacologically active study drug (not dummy placebo)
Key: bid = twice daily; od = once daily; SC = subcutaneous
Sponsor's table

Four RECORD studies used the same inclusion and exclusion criteria except few indicated below.

Inclusion criteria

- Men and women aged ≥18 years.
- Subjects scheduled for elective total hip replacement (RECORD 1 and 2) or total knee replacement surgery (RECORD 3-4).
- Subjects giving written informed consent for participation after receiving detailed written and oral information prior to any study specific procedures.

Exclusion criteria

- Planned, staged total bilateral hip replacement (RECORD 1 and 2 only).

- Active bleeding or high risk of bleeding contraindicating treatment with low molecular-weight heparin.
- Significant liver disease (eg acute clinical hepatitis, chronic active hepatitis, cirrhosis) (*modified in Amendment 1).*
- Contraindication listed in the labeling or conditions precluding subject treatment with enoxaparin requiring dose adjustment (e.g. severe renal impairment; refer to the local label of enoxaparin of the respective country) (*modified in Amendment 1).*
- Conditions prohibiting bilateral venography (amputation of 1 leg, allergy to contrast media).
- Pregnant and breast-feeding women. Women with child-bearing potential not using adequate birth control method. (Note: as adequate method of birth control oral contraception was recommended. If oral contraception was not feasible, both partners were to use adequate barrier birth control).
- Drug or alcohol abuse.
- Concomitant use of HIV-protease inhibitors or fibrinolytics.
- Therapy with another investigational product within 30 days prior start of study.
- Planned intermittent pneumatic compression during active treatment period.
- Concomitant participation in another trial or study.
- Ongoing oral anticoagulant therapy that could not be stopped in the opinion of the investigator.
- Treatment with strong inhibitors of cytochrome P450 3A4, such as ketoconazole or protease inhibitors, within 4 days before randomization, or planned treatment during the time period of the study (modified text per Amendment 1) (RECORD 4 only)

All four studies used the same primary and secondary efficacy endpoints as specified below.

The primary efficacy endpoint was a composite endpoint of

- Any deep vein thrombosis (DVT) (proximal and/or distal)
- Non-fatal pulmonary embolism (PE)
- Death from all causes.

The pre-specified secondary efficacy endpoints were:

- Major VTE (proximal DVT, non-fatal PE, VTE-related death) as main secondary endpoint.
- Incidence of DVT (total, proximal, distal).
- Incidence of symptomatic VTE (DVT, PE).
- Incidence of symptomatic VTE during follow-up (i.e., after the end of the time window for primary efficacy assessment).
- "Net clinical benefit" assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding.
- Incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death (composite of any DVT and non-fatal PE and VTE-related death).

- Incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death (composite of proximal DVT and non-fatal PE and death from all causes).

Asymptomatic DVT was assessed by bilateral venography at the end of study treatment. In case of a suspected symptomatic DVT, an ultrasound was to be performed first. If a DVT was confirmed by ultrasound, a venography has to be performed. If symptoms of PE occur, pulmonary angiography or a perfusion/Ventilation lung scintigraphy combined with chest radiography or spiral CT were performed. The analysis of the primary efficacy endpoint and all secondary efficacy endpoints related to VTE was based solely on the assessments made by the Independent Central Adjudication Committee (ICAC) and VTE Adjudication Committees (AC/VTE).

The efficacy of rivaroxaban was to be assessed in 2 steps. First, a non-inferiority test as described below was to be performed based on the per protocol population. If non-inferiority was shown, a superiority test was performed subsequently based on the modified intent to treat (MITT) population.

RECORD 2 and 3 were designed as superiority trials and a superiority test was performed based on the MITT population.

MITT population included study patients who received at least one dose of study medication, underwent the appropriate surgery, and had an adequate assessment of VTE.

The safety assessment was the same in all 4 RECORD studies.

The primary safety endpoint in each study was the incidence of treatment-emergent major bleeding observed not later than 2 days after the last administration of study drug. Major bleeding events were defined as:

- Fatal bleeding
- Bleeding into critical organ (e.g., retroperitoneal, intracranial, intraocular or intraspinal bleeding/hemorrhagic puncture)
- Bleeding requiring reoperation
- Clinically overt extra-surgical site bleeding associated with ε 2 g/dL fall in hemoglobin
- Clinically overt extra-surgical site bleeding leading to infusion of equal or more than 2 units of whole blood or packed cells

Any bleeding and non-major clinical relevant bleedings were also assessed in each study. Non-major clinically relevant bleeding events were defined in the protocol as:

- Multiple source bleeding
- Spontaneous hematoma >25 cm^2
- Excessive wound hematoma
- Spontaneous nose bleeding lasting for >5 minutes
- Gingival bleeding >5 minutes

- Macroscopic hematuria (spontaneous or lasting more than 24 hours, if associated with an intervention)
- Spontaneous rectal bleeding (more than a spot on toilet paper)
- Coughing blood (hemoptysis)
- Hematemesis
- Prolonged bleeding after venipuncture >5 minutes

Other interested adverse events included cardiovascular events and hepatic events.

Liver function tests (LFTs) were monitored at Days 1, 6, 13, 36 (RECORD 1 and 2 only), 42 (RECORD 3 and 4 only), and 65 (RECORD 1 and 2 only).

Safety analysis was based on safety population that included study patients who received at least one dose of study medication.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is for the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing:

- hip replacement surgery
- knee replacement surgery.

6.1.1 Methods

Four randomized controlled pivotal trials were reviewed for efficacy for the proposed indications. These included two studies (RECORD 1 and 2) in patients undergoing total hip replacement surgery (THR) and two studies (RECORD 3 and 4) in patients undergoing total knee replacement surgery (TKR). All four clinical studies were randomized, double-blind, double-dummy, active-controlled studies. Enoxaparin was used as active control treatment for all studies. Two trials (RECORD 2 and 3) were designed as superiority trials and two trials (RECORD 1 and 4) were designed as non-inferiority trials.

In all 4 RECORD trials, Rivaroxaban was administered at a dose of 10 mg once daily at least 6 to 8 hours after surgery (wound closure) after elective THR or TKR surgery. The treatment duration of Rivaroxaban was 35 days for patients undergoing THR and 13 days for patients undergoing TKR.

The enoxaparin dosing regimen in RECORD 1 (11354), RECORD 2 (11357) and RECORD 3 (11356) was 40 mg once daily starting 12 hours preoperatively. The enoxaparin regimen in

RECORD 4 (11355) was 30 mg twice daily starting 12 to 24 hours postoperatively. It should be noted that enoxaparin dose regimen (40 mg once daily) in RECORD 3 study is not an approved dose regimen of enoxaparin for the prophylaxis of DVT in patients undergoing TKR surgery in United States.

It should be noted that the treatment duration was much longer in the rivaroxaban group (35 days) as compared to enoxaparin control (12 days) in RECORD 2 study.

The following table shows the number of randomized patients in each trial.

Number of randomized patients and treatment duration in RECORD studies

Studies	Rivaroxaban 10 mg OD	Enoxaparin 40 mg OD/30 mg BID
THR (Study treatment for 35 days)		
RECORD 1	2266	2275
RECORD 2	1252	1257 (Enoxaparin for 13 days followed by placebo for 23 days)
TKR (Study treatment for 12 days)		
RECORD 3	1254	1277 (40mg QD-unapproved dose regimen)
RECORD 4	1584	1564
Total	**6356**	**6373**

Reviewer's table

6.1.2 Demographics and baseline characteristics

The following table shows the demographic characteristics of study patients in RECORD studies. There were more females (60%) than males (40%). The mean age was 64 years with about one half of study patients over 65 years. The majority of study patients were Caucasians with 10% of Asians and 10% of other races.

	THR RECORD 1-2 (N=6890)	TKR RECORD 3-4 (N=5493)	Total (N=12383)
Gender			
Male	3110 (45%)	1841 (34%)	4951 (40%)

Female	3780 (55%)	3652 (66%)	7432 (60%)
Age (years)	62.6 ±12.2	65.9 ±9.5	64.1 ±11.2
Age			
<65 yrs	3532 (51%)	2288 (42%)	5820 (47%)
65-75 yrs	2460 (36%)	2275 (41%)	4735 (38%)
>75 yrs	898 (14%)	930 (17%)	1828 (15%)
Race			
White	5687 (83%)	4037 (73%)	9724 (79%)
Black	103 (1%)	181 (3%)	284 (2%)
Asian	498 (7%)	736 (13%)	1234 (10%)
Hispanic	329 (5%)	353 (6%)	682 (6%)
Other or missing	273 (4%)	186 (4%)	459 (4%)

6.1.3 Patient Disposition

The following table shows the patient disposition in RECORD 1 and 2 studies in patients undergoing total hip replacement surgery. More than 87% of patients completed the study and 11-13% of patients had premature termination. The main reasons for premature termination were consent withdrawal (4-5%) and adverse events (4%). The distribution of patient disposition was similar between the rivaroxaban and enoxaparin treatment groups.

Patient Disposition in THR Trials

	RECORD 1		RECORD 2	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Randomized	2266	2275	1252	1257
Completed	2010 (88.7%)	2011 (88.4%)	1117 (89.2%)	1092 (86.9%)
Premature termination	256 (11.3%)	264 (11.6%)	135 (10.8%)	165 (13.1%)
-AE	82 (3.6%)	92 (4.0%)	44 (3.5%)	54 (4.3%)
-Consent withdrawn	121 (5.3%)	115 (5.1%)	51 (4.1%)	51 (4.1%)

The following table shows the patient disposition in RECORD 3 and 4 studies in patients undergoing total knee replacement surgery. More than 88% of patients completed the study and 10-12% of patients had premature termination. The main reasons for premature termination were

consent withdrawal (3-5%) and adverse events (3-4%). The distribution of patient disposition was similar between the rivaroxaban and enoxaparin treatment groups.

Patient Disposition in TKR Trials

	RECORD 3		RECORD 4	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Randomized	1254	1277	1584	1564
Completed	1127 (89.9%)	1122 (87.9%)	1425 (90.0%)	1413 (90.4%)
Premature termination	127 (10.1%)	155 (12.1%)	159 (10.0%)	151 (9.6%)
-AE	36 (2.9%)	42 (3.3%)	62 (3.9%)	56 (3.6%)
-Consent withdrawn	68 (5.4%)	60 (4.7%)	49 (3.1%)	47 (3.0%)

The following table shows the study patients who were included in the MITT population for the primary efficacy analysis. Overall, about one third of randomized patients were excluded from the MITT population in RECORD studies with the highest in RECORD 4 study (39%).

Patients were included in the MITT Population

Studies	**Rivaroxaban 10 mg OD**	**Enoxaparin 40 mg OD/30 mg BID**
THR		
RECORD 1	1595 (70%)	1558 (69%)
RECORD 2	864 (69%)	869 (69%)
TKR		
RECORD 3	824 (66%)	878 (69%)
RECORD 4	965 (61%)	959 (61%)
Total	4248 (67%)	4264 (67%)

The reasons for exclusion from the MITT population in RECORD 1 and 2 in patients undergoing THR are shown below. The majority of excluded patients had no adequate assessment of DVT due to venography not done (50%), unilateral venography (17%), and venography too early or late (3-7%). These were similar between the two treatment groups.

Reasons for Excluded from MITT population in THR Trials

	RECORD 1		RECORD 2	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Excluded from MITT pop.	671 (30%)	711 (32%)	388 (31%)	388 (31%)
No surgery	17 (1%)	21 (1%)	16 (1%)	22 (2%)
No treatment	57 (3%)	51 (2%)	24 (2%)	28 (2%)
No adequate assessment	588 (26%)	635 (28%)	348 (28%)	338 (27%)
-Venography not done	319 (54%)	322 (51%)	155 (45%)	159 (47%)
-Unilateral venography	105 (18%)	105 (17%)	57 (16%)	57 (17%)
-Unevaluable venography	121 (21%)	164 (26%)	127 (37%)	111 (33%)
-Venography too early/late	43 (7%)	44 (7%)	9 (3%)	11 (3%)

The reasons for exclusion from the MITT population in RECORD 3 and 4 in patients undergoing TKR are shown below. The reasons were similar to RECORD 1 and 2 studies with more patients who had no adequate assessment of DVT in RECORD 4 study (35%) mostly due to unevaluable venography.

Reasons for Excluded from MITT population in TKR Trials

	RECORD 3		RECORD 4	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Excluded from MITT pop.	430 (34%)	399 (31%)	619 (39%)	605 (39%)
No surgery	20 (2%)	22 (2%)	2 (<1%)	3 (<1%)
No treatment	34 (3%)	38 (3%)	58 (4%)	56 (4%)
No adequate assessment	376 (30%)	339 (27%)	559 (35%)	546 (35%)
-Venography not done	156 (41.5%)	166 (49.0%)	189 (34%)	184 (34%)
-Unilateral venography	82 (21.8%)	69 (20.4%)	116 (21%)	105 (19%)
-Unevaluable venography	131 (34.8%)	96 (28.3%)	244 (44%)	253 (46%)
-Venography too early/late	7 (1.9%)	8 (2.3%)	10 (2%)	4 (<1%)

The main reasons for venography not done were failed venipuncture, subject refused venography and premature termination in each study (see Tables below). The reasons were similar between the two treatment groups.

Reasons for Venography Not Done in THR Trials

	RECORD 1		**RECORD 2**	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Venography not done	319 (54%)	322 (51%)	155 (45%)	159 (47%)
-Failed venipuncture	60 (10.2%)	65 (10.2%)	37 (10.6%)	28 (8.3)
-Subject refused venography	73 (12.4%)	64 (10.1%)	13 (3.7%)	8 (2.4%)
-Premature termination	147 (25.0%)	165 (26.0%)	85 (24.4%)	93 (27.5%)

Reasons for Venography Not Done in TKR Trials

	RECORD 3		**RECORD 4**	
	Rivaroxaban	Enoxaparin	Rivaroxaban	Enoxaparin
Venography not done	156 (41.5%)	166 (49.0%)	189 (34%)	184 (34%)
-Failed venipuncture	38 (10.1%)	43 (12.7%)	68 (12.2%)	65 (11.9%)
-Subject refused venography	32 (8.5%)	30 (8.8%)	34 (6.1%)	34 (6.2%)
-Premature termination	59 (15.7%)	67 (19.8%)	70 (12.5%)	60 (11.0%)

The following tables show the demographics in MITT population in each RECORD study by study treatment. There were similar demographical distributions between the two treatment groups in each study.

Demographics in MITT population in RECORD 1 study

Demographic variable	Rivaroxaban 10 mg od (n=1595) n (%)	Enoxaparin 40 mg od (n=1558) n (%)	Total (n=3153) n (%)
Sex, n (%)			
Male	745 (46.7)	710 (45.6)	1455 (46.1)
Female	850 (53.3)	848 (54.4)	1698 (53.9)
Race, n (%)			
Missing	74 (4.6)	73 (4.7)	147 (4.7)
White	1491 (93.5)	1452 (93.2)	2943 (93.3)
Black	11 (0.7)	13 (0.8)	24 (0.8)
Asian	2 (0.1)	2 (0.1)	4 (0.1)
American Indian	1 (<0.1)	0 ((0.0)	1 (<0.1)
Hispanic	12 (0.8)	11 (0.7)	23 (0.7)
Uncodable	4 (0.3)	7 (0.4)	11 (0.3)
Age (years)			
Missing	0	0	0
Mean ± SD	62.4 ± 11.4	63.1 ± 11.1	62.7 ± 11.2
Range	18.0 – 91.0	20.0 – 89.0	18.0 – 91.0
Age (categorized)			
18 to 40 years	72 (4.5)	54 (3.5)	126 (4.0)
>40 to <65 years	776 (48.7)	743 (47.7)	1519 (48.2)
65 to 75 years	579 (36.3)	569 (36.5)	1148 (36.4)
>75 years	168 (10.5)	192 (12.3)	360 (11.4)
Weight (kg)			
Missing	1	2	3
Mean ± SD	78.2 ± 15.8	78.1 ± 15.6	78.2 ± 15.7
Range	37.0 – 158.8	40.0 – 130.0	37.0 – 158.8
Weight (categorized), n (%)			
Missing	1 (<0.1)	2 (0.1)	3 (<0.1)
≤50 kg	36 (2.3)	39 (2.5)	75 (2.4)
>50 to 70 kg	506 (31.7)	482 (30.9)	988 (31.3)
>70 to 90 kg	726 (45.5)	716 (46.0)	1442 (45.7)
>90 to 110 kg	280 (17.6)	278 (17.8)	558 (17.7)
>110 kg	46 (2.9)	41 (2.6)	87 (2.8)
BMI (kg/m^2)			
Missing	4	3	7
Mean ± SD	27.8 ± 4.6	27.7 ± 4.6	27.7 ± 4.6
Range	16.2 – 53.4	15.2 – 50.2	15.2 – 53.4
BMI (categorized), n (%)			
Missing	4 (0.3)	3 (0.2)	7 (0.2)
<18.5 kg/m^2	13 (0.8)	19 (1.2)	32 (1.0)
18.5 to <25 kg/m^2	427 (26.8)	430 (27.6)	857 (27.2)
25 to <30 kg/m^2	694 (43.5)	676 (43.4)	1370 (43.5)
30 to <40 kg/m^2	431 (27.0)	417 (26.8)	848 (26.9)
≥40 kg/m^2	26 (1.6)	13 (0.8)	39 (1.2)
Current alcohol consumption, n (%)			
Missing	7 (0.4)	4 (0.3)	11 (0.3)
Abstinent	630 (39.5)	683 (43.8)	1313 (41.6)
Light alcohol consumption	836 (52.4)	730 (46.9)	1566 (49.7)
Moderate alcohol consumption	122 (7.7)	138 (8.9)	260 (8.3)
Heavy alcohol consumption	0 (0.0)	3 (0.2)	3 (0.1)

Abbreviations: BMI=body mass index; MITT=modified intent-to-treat; od=once daily; SD=standard deviation

Demographics in MITT population in RECORD 2 study

Demographic variable	Rivaroxaban 10 mg od (N=864) n (%)	Enoxaparin 40 mg od (N=869) n (%)	Total (N=1733) n (%)
Sex, n (%)			
Male	409 (47)	415 (48)	824 (48)
Female	455 (53)	454 (52)	909 (52)
Race, n (%)			
White	564 (65)	543 (62)	1107 (64)
Black	18 (2)	16 (2)	34 (2)
Asian	177 (20)	182 (21)	359 (21)
American Indian	1 (<1)	1 (<1)	2 (<1)
Hispanic	96 (11)	116 (13)	212 (12)
Uncodable	8 (1)	11 (1)	19 (1)
Age (years)			
Missing	0	0	0
Mean ± SD	61.2 ±12.9	61.0 ±13.7	61.1 ±13.3
Range	19.0 – 91.0	20.0 – 93.0	19.0 – 93.0
Age (categorized)			
18 to 40 years	63 (7.3)	79 (9.1)	142 (8.2)
>40 to <65 years	407 (47.1)	401 (46.1)	808 (46.6)
65 to 75 years	302 (35.0)	285 (32.8)	587 (33.9)
>75 years	92 (10.7)	104 (12.0)	196 (11.3)
Weight (kg)			
Missing	0	0	0
Mean ± SD	74.3 ±15.3	74.3 ±16.9	74.3 ±16.1
Range	41.0 – 140.0	33.2 – 151.0	33.2 – 151.0
Weight (categorized), n (%)			
≤50 kg	40 (4.6)	55 (6.3)	95 (5.5)
>50 to 70 kg	361 (41.8)	346 (39.8)	707 (40.8)
>70 to 90 kg	333 (38.5)	336 (38.7)	669 (38.6)
>90 to 110 kg	121 (14.0)	107 (12.3)	228 (13.2)
>110 kg	9 (1.0)	25 (2.9)	34 (2.0)
BMI (kg/m^2)			
Missing	0	1	1
Mean ± SD	26.6 ±4.5	26.7 ±4.9	26.7 ±4.7
Range	15.6 – 50.9	15.5 – 59.0	15.5 – 59,0
BMI (categorized), n (%)			
Missing	0 (0.0)	1 (0.1)	1 (0.1)
<18.5 kg/m^2	11 (1.3)	23 (2.7)	34 (2.0)
18.5 to <25 kg/m^2	322 (37.3)	320 (36.8)	642 (37.1)
25 to <30 kg/m^2	362 (41.9)	329 (37.9)	691 (39.9)
30 to <40 kg/m^2	160 (18.5)	185 (21.3)	345 (19.9)
≥40 kg/m^2	9 (1.0)	11 (1.3)	20 (1.2)
Current alcohol consumption, n (%)			
Missing	0 (0.0)	1 (0.1)	1 (0.1)
Abstinent	393 (45.5)	399 (45.9)	792 (45.7)
Light alcohol consumption	393 (45.5)	372 (42.8)	765 (44.1)
Moderate alcohol consumption	77 (8.9)	96 (11.1)	173 (10.0)
Heavy alcohol consumption	1 (0.1)	1 (0.1)	2 (0.1)

Abbreviations: BMI=body mass index; MITT=modified intent-to-treat; od=once daily; SD=standard deviation

Demographics in MITT population in RECORD 3 study

Demographic variable	Rivaroxaban 10 mg od (N=824)	Enoxaparin 40 mg od (N=878)	Total (N=1702)
Sex, n (%)			
Male	259 (31.4)	314 (35.8)	573 (33.7)
Female	565 (68.6)	564 (64.2)	1129 (66.3)
Race, n (%)			
Missing	41 (5.0)	50 (5.7)	91 (5.4)
White	675 (81.9)	668 (78.4)	1363 (80.1)
Black	8 (1.0)	8 (0.9)	16 (0.9)
Asian	64 (7.8)	68 (7.7)	132 (7.8)
Hispanic	33 (4.0)	48 (5.5)	81 (4.8)
Uncodable	3 (0.4)	16 (1.8)	19 (1.1)
Age (yr)			
Mean ± SD	67.4 ± 9.0	67.2 ± 8.6	67.6 ± 9.0
Range	28 – 87	30 – 87	28 - 87
Age (categorized)			
18 to 40 yr	4 (0.5)	1 (0.1)	5 (0.3)
> 40 to < 65 yr	282 (34.2)	318 (36.2)	600 (35.3)
65 to 75 yr	365 (44.3)	402 (45.8)	767 (45.1)
> 75 yr	173 (21.0)	157 (17.9)	330 (19.4)
Weight (kg)			
N	823	877	1700
Missing	1	1	2
Mean ± SD	80.0 ± 14.8	81.0 ± 15.0	80.5 ± 14.9
Range	46 - 150	48 – 150	46 - 150
Weight (categorized), n (%)			
Missing	1 (0.1)	1 (0.1)	2 (0.1)
≤ 50 kg	11 (1.3)	6 (0.7)	17 (1.0)
> 50 to 70 kg	237 (28.8)	220 (25.1)	457 (26.9)
> 70 to 90 kg	388 (47.1)	437 (49.8)	825 (48.5)
> 90 to 110 kg	163 (19.8)	180 (20.5)	343 (20.2)
> 110 kg	24 (2.9)	34 (3.9)	58 (3.4)
BMI (kg/m^2)			
N	823	877	1700
Missing	1	1	2
Mean ± SD	29.3 ± 4.8	29.7 ± 4.8	29.5 ± 4.8
Range	16.9 – 48.4	17.7 – 53.3	16.9 – 53.3
BMI (categorized), n (%)			
Missing	1 (0,1)	1 (0.1)	2 (0.1)
< 18.5 kg/m^2	4 (0.5)	1 (0.1)	5 (0.3)
18.5 to < 25 kg/m^2	133 (16.1)	121 (13.8)	254 (14.9)
25 to < 30 kg/m^2	359 (43.6)	400 (45.6)	759 (44.6)
30 to < 40 kg/m^2	307 (37.3)	325 (37.0)	632 (37.1)
≥ 40 kg/m^2	20 (2.4)	30 (3.4)	50 (2.9)

Abbreviations: BMI=body mass index; MITT=modified intent to treat; od=once daily; SD=standard deviation; and yr=year

Demographics in MITT population in RECORD 4 study

Demographic variable	Rivaroxaban 10 mg od (N=965)	Enoxaparin 30 mg bid (N=959)	Total (N=1924)
Sex, n (%)			
Male	343 (35.5)	353 (36.8)	696 (36.2)
Female	622 (64.5)	606 (63.2)	1228 (63.8)
Race, n (%)			
Missing	1 (0.1)	0	1 (<0.1)
White	671 (69.5)	683 (71.2)	1354 (70.4)
Black	48 (5.0)	42 (4.4)	90 (4.7)
Asian	156 (16.2)	149 (15.5)	305 (15.8)
American Indian	0	4 (0.4)	4 (0.2)
Hispanic	88 (9.1)	80 (8.3)	168 (8.7)
Uncodable	1 (0.1)	1 (0.1)	2 (0.1)
Age (yr)			
Mean ± SD	64.4 ± 9.9	64.6 ± 9.7	64.5 ± 9.8
Range	21 – 87	24 – 89	21 - 89
Age (categorized)			
18 to 40 yr	12 (1.2)	10 (1.0)	22 (1.1)
> 40 to < 65 yr	465 (48.2)	435 (45.4)	900 (46.8)
65 to 75 yr	338 (35.0)	390 (40.7)	728 (37.8)
> 75 yr	150 (15.5)	124 (12.9)	274 (14.2)
Weight (kg)			
N	965	959	1924
Missing	0	0	0
Mean ± SD	84.5 ± 19.8	85.0 ± 20.5	84.7 ± 20.1
Range	41 – 163.3	35 – 171.5	35 – 171.5
Weight (categorized), n (%)			
Missing	0	0	0
≤ 50 kg	13 (1.4)	19 (2.0)	32 (1.7)
> 50 to 70 kg	235 (24.4)	218 (22.7)	453 (23.5)
> 70 to 90 kg	386 (40.0)	385 (40.2)	771 (40.1)
> 90 to 110 kg	221 (22.9)	225 (23.5)	446 (23.2)
> 110 kg	110 (11.4)	112 (11.7)	222 (11.5)
BMI (kg/m^2)			
N	965	959	1924
Missing	0	0	0
Mean ± SD	30.7 ± 5.9	30.7 ± 5.9	30.7 ± 5.9
Range	17.9 – 56.0	13.7 – 53.6	13.7 – 56.0
BMI (categorized), n (%)			
Missing	0	0	0
< 18.5 kg/m^2	1 (0.1)	4 (0.4)	5 (0.3)
18.5 to < 25 kg/m^2	142 (14.7)	138 (14.4)	280 (14.6)
25 to < 30 kg/m^2	341 (35.3)	341 (35.6)	682 (35.4)
30 to < 40 kg/m^2	405 (42.0)	396 (41.3)	801 (41.6)
≥ 40 kg/m^2	76 (7.9)	80 (8.3)	156 (8.1)

Abbreviations: BMI=body mass index; enoxaparin 30 mg bid=enoxaparin 30 mg q 12h ± 2h; MITT=modified intent to treat; od=once daily; SD=standard deviation; and yr=year

6.1.4 Analysis of Primary Endpoint

In patients undergoing total hip replacement surgery

The following table shows the efficacy results for the primary efficacy endpoint of total VTE and its components from RECORD 1 and 2 trials based on MITT population.

RECORD 1 study was designed as a non-inferiority trial with a stepwise approach. The efficacy of rivaroxaban was assessed by a non-inferiority test based on the per protocol population (PP) first and if non-inferiority was shown, a superiority test was performed subsequently based on the MITT population. In the PP population analysis, total VTE occurred in 13 (0.9%) and 50 (3.4%) subjects randomized to rivaroxaban or enoxaparin, respectively; which showed non-inferiority (95% CI: -3.55%, -1.51%) of rivaroxaban 10 mg once daily as compared to enoxaparin 40 mg once daily.

In RECORD 1 study based on MITT population, the total VTE was 1.1% in the rivaroxaban group as compared to 3.7% in the enoxaparin control group. The difference in the total VTE rate between the two treatment groups was statistically significant ($p<0.001$). The difference between the two treatment groups was mainly due to proximal and distal DVT. It should be noted that there were 4 (0.5%) non-fatal PE in the Rivaroxaban group as compared to 1 (0.1%) in the enoxaparin group.

In RECORD 2 study, the treatment duration was more than twice as long in the Rivaroxaban group (35 days) as in the enoxaparin control group (13 days). The total VTE was lower in the Rivaroxaban group (2.0%) as compared to the enoxaparin group (9.3%). The difference in the total VTE rate between the two treatment groups was statistically significant ($p<0.001$). The difference between the 2 treatment groups was mainly due to proximal and distal DVT. There were also fewer deaths and nonfatal PE in the Rivaroxaban group than in the enoxaparin control group. The difference in the total VTE rate between the two treatment groups may largely be due to the different treatment durations (rivaroxaban 35 days vs. enoxaparin 13 days) between the two treatment groups.

Efficacy Results in THR Trials: Primary Efficacy Endpoint in MITT population

	RECORD 1		**RECORD 2**	
Endpoint	Rivaroxaban 10mg qd N=1595	Enoxaparin 40mg qd N=1558	Rivaroxaban 10mg qd N=864	Enoxaparin 40 mg qd + Placebo N=869
Total VTE	18 (1.1%)[a]	58 (3.7%)	17 (2.0%)[a]	81 (9.3%)
All cause death	4 (0.3%)	4 (0.3%)	2 (0.2%)	6 (0.7%)

Nonfatal PE	4 (0.3%)	1 (<0.1%)	1 (0.1%)	4 (0.5%)
Proximal DVT	1 (<0.1%)	31 (2.0%)	5 (0.6%)	44 (5.1%)
Distal DVT	12 (0.8%)	27 (1.7%)	11 (1.3%)	49 (5.6%)

a: p<0.001

In patients undergoing total knee replacement surgery

The following table shows the efficacy results for the primary efficacy endpoint of total VTE and its components from RECORD 3 and 4 trials based on MITT population.

The RECORD 4 study was designed as a non-inferiority trial with a stepwise approach. The efficacy of rivaroxaban was assessed by a non-inferiority test based on the PP population first and if non-inferiority was shown, a superiority test was performed subsequently based on the MITT population. In the PP population analysis, total VTE occurred in 58 (6.7%) and 82 (9.3%) of subjects randomized to rivaroxaban or enoxaparin, respectively; which showed non-inferiority (95% CI: -5.25%, -0.17%) of rivaroxaban 10 mg once daily as compared to enoxaparin 30 mg twice daily.

In the RECORD 3 study the enoxaparin dosing regimen used (40 mg once daily) is not an approved dosing regimen for the prophylaxis of DVT in patients undergoing total knee replacement surgery in United States. Based on MITT population, the total VTE was 9.6% in the rivaroxaban group as compared to 18.9% in the enoxaparin group. The difference in the total VTE rate between the two treatment groups was statistically significant (p<0.001). The difference between the two treatment groups was mainly due to distal DVT. There were also fewer deaths, nonfatal PE and proximal DVT in the Rivaroxaban group than in the enoxaparin group.

In the RECORD 4 study based on MITT population, the total VTE was lower in the Rivaroxaban group (6.9%) as compared to the enoxaparin group (10.1%). The difference in the total VTE rate between the two treatment groups was statistically significant (p<0.05). Similar to RECORD 2, the difference between the 2 treatment groups was mainly due to the distal DVT. There were also fewer deaths and nonfatal PE in the Rivaroxaban group than in the enoxaparin control group.

Efficacy Results in TKR Trials: Primary Efficacy Endpoint in MITT population

	RECORD 3		**RECORD 4**	
Endpoint	Rivaroxaban 10mg qd N=824	Enoxaparin 40mg qd N=878	Rivaroxaban 10mg qd N=965	Enoxaparin 30mg bid N=959

Total VTE	79 (9.6%)[a]	166 (18.9%)	67 (6.9%)[b]	97 (10.1%)
All cause death	0	2 (0.2%)	2 (0.2%)	3 (0.3%)
Nonfatal PE	0	4 (0.5%)	5 (0.5%)	8 (0.8 %)
Proximal DVT	9 (1.1 %)	20 (2.3%)	8 (0.8%)	14 (1.5%)
Distal DVT	74 (9.0 %)	156 (17.8%)	57 (5.9%)	82 (8.6%)

a: $p<0.001$; b: $p=0.012$

Sensitivity analysis

The following table shows the sensitivity analysis for the primary efficacy endpoint in the RECORD studies. It used different scenarios for handling missing responses in the subjects invalidated due to no adequate assessment of DVT in all randomized population.

All analyses showed statistical superiority of the rivaroxaban as compared to the enoxaparin with the exception of the pessimistic scenario in RECORD 3 and 4 studies.

Sensitivity Analysis in RECORD 1-4 Studies

RECORD 1

Primary efficacy endpoint				
Observed cases [b]				
Rivaroxaban 10 mg od	20/2266	(0.9%)	-1.90%	[-2.67%, -1.12%]
Enoxaparin 40 mg od	63/2275	(2.8%)		
Realistic scenario [c]				
Rivaroxaban 10 mg od	24/2266	(1.1%)	-2.46%	[-3.32%, -1.60%]
Enoxaparin 40 mg od	80/2275	(3.5%)		
Optimistic scenario [d]				
Rivaroxaban 10 mg od	18/2266	(0.8%)	-1.80%	[-2.55%, -1.06%]
Enoxaparin 40 mg od	59/2275	(2.6%)		
Pessimistic scenario [e]				
Rivaroxaban 10 mg od	689/2266	(30.4%)	-3.49%	[-6.14%, -0.84%]
Enoxaparin 40 mg od	775/2275	(34.1%)		
Adjudicated and non-assessable findings [f]				
Rivaroxaban 10 mg od	21/2266	(0.9%)	-1.76%	[-2.53%, -0.99%]
Enoxaparin 40 mg od	61/2275	(2.7%)		

RECORD 2

Primary efficacy endpoint				
Observed cases [b]				
Rivaroxaban 10 mg od	21/1252	(1.68%)	-5.01%	[-6.55%, -3.47%]
Enoxaparin 40 mg od	84/1257	(6.68%)		
Realistic scenario [c]				
Rivaroxaban 10 mg od	24/1252	(1.92%)	-6.68%	[-8.39%, -4.98%]
Enoxaparin 40 mg od	108/1257	(8.59%)		
Optimistic scenario [d]				
Rivaroxaban 10 mg od	18/1252	(1.44%)	-5.01%	[-6.51%, -3.51%]
Enoxaparin 40 mg od	81/1257	(6.44%)		
Pessimistic scenario [e]				
Rivaroxaban 10 mg od	405/1252	(32.25%)	-5.01%	[-8.65%, -1.37%]
Enoxaparin 40 mg od	469/1257	(37.31%)		
Adjudicated and non-assessable findings [f]				
Rivaroxaban 10 mg od	23/1252	(1.84%)	-5.01%	[-6.58%, -3.44%]
Enoxaparin 40 mg od	86/1257	(6.84%)		

RECORD 3

Primary efficacy endpoint				
Observed cases[b]				
Rivaroxaban 10 mg od	85/1254	(6.8%)	-6.62%	[-8.94%, -4.31%]
Enoxaparin 40 mg od	171/1277	(13.4%)		
Realistic scenario[c]				
Rivaroxaban 10 mg od	122/1254	(9.7%)	-8.43%	[-11.07%, -5.79%]
Enoxaparin 40 mg od	232/1277	(18.2%)		
Optimistic scenario[d]				
Rivaroxaban 10 mg od	79/1254	(6.3%)	-6.71%	[-8.98%, -4.45%]
Enoxaparin 40 mg od	166/1277	(13.0%)		
Pessimistic scenario[e]				
Rivaroxaban 10 mg od	509/1254	(40.6%)	-3.56%	[-7.33%, 0.20%]
Enoxaparin 40 mg od	565/1277	(44.2%)		
Adjudicated and nonassessable findings[f]				
Rivaroxaban 10 mg od	82/1254	(6.5%)	-6.71%	[-9.01%, -4.42%]
Enoxaparin 40 mg od	169/1277	(13.2%)		

RECORD 4

Primary efficacy endpoint				
Observed cases[b]				
Rivaroxaban 10 mg od	75/1584	(4.7%)	-1.79%	[-3.40%, -0.18%]
Enoxaparin 30 mg bid	102/1564	(6.5%)		
Realistic scenario[c]				
Rivaroxaban 10 mg od	104/1584	(6.6%)	-2.39%	[-4.25%, -0.53%]
Enoxaparin 30 mg bid	140/1564	(9.0%)		
Optimistic scenario[d]				
Rivaroxaban 10 mg od	67/1584	(4.2%)	-1.98%	[-3.52%, -0.43%]
Enoxaparin 30 mg bid	97/1564	(6.2%)		
Pessimistic scenario[e]				
Rivaroxaban 10 mg od	686/1584	(43.3%)	-1.57%	[-5.03%, 1.89%]
Enoxaparin 30 mg bid	702/1564	(44.9%)		
Adjudicated and nonassessable findings[f]				
Rivaroxaban 10 mg od	68/1584	(4.3%)	-2.10%	[-3.67%, -0.54%]
Enoxaparin 30 mg bid	100/1564	(6.4%)		

b Subjects without adequate assessment due to either too early or too late assessments were included
c Within a geographic region, subjects without adequate assessment of thromboembolism were assumed to have the same risk for asymptomatic DVT as the subjects with adequate assessment belonging to the same treatment group
d None of the subjects without adequate assessment of thromboembolism were assumed to be a treatment failure (i.e., have an event)
e Subjects without adequate assessment of thromboembolism were assumed to be a treatment failure (i.e., have an event)
f In addition to adjudicated findings, symptomatic findings reported by the investigator that were deemed non-assessable by the VTE adjudication committee were included, if finding occurred within the time window

6.1.5 Analysis of Secondary Endpoints

Main Secondary Efficacy Endpoint

Major VTE was a pre-specified main secondary efficacy endpoint in the RECORD studies. The following table shows the major VTE endpoint and its components in RECORD 1 and 2 trials in MITT population in patients undergoing THR surgery. The major VTE rate was lower in the Rivaroxaban group as compared to control in both studies.

Major VTE in MITT population in THR Trials

	RECORD 1		**RECORD 2**	
Endpoint	Rivaroxaban 10mg qd N=1686	Enoxaparin 40mg qd N=1678	Rivaroxaban 10mg qd N=961	Enoxaparin 40 mg qd + Placebo N=962
Major VTE	4 (0.2%)[a]	33 (2.0%)	6 (0.6%)[a]	49 (5.1%)
VTE-related death	0	1 (<0.1%)	0	1 (0.1%)
Nonfatal PE	4 (0.2%)	1 (<0.1%)	1 (0.1%)	4 (0.4%)
Proximal DVT	1 (<0.1%)	31 (1.9%)	5 (0.5%)	44 (4.6%)

a: $p<0.001$

The following table shows major VTE and its components in RECORD 3 and 4 trials in MITT population in patients undergoing TKR surgery. The major VTE rate was lower in the Rivaroxaban group as compared to control in RECORD 3 study. The difference in the major VTE rate between the two treatment groups was not statistically significant in the RECORD 4 trial ($p>0.05$).

Major VTE in MITT population in TKR Trials

	RECORD 3		RECORD 4	
Endpoint	Rivaroxaban 10mg qd N=908	Enoxaparin 40mg qd N=925	Rivaroxaban 10mg qd N=1122	Enoxaparin 30mg bid N=1112
Major VTE	9 (1.0%)[a]	24 (2.6%)	13 (1.2%)[b]	22 (2.0%)
VTE-related death	0	0	1 (0.1%)	0
Nonfatal PE	0	4 (0.4%)	5 (0.5%)	8 (0.7 %)
Proximal DVT	9 (1.0 %)	20 (2.2%)	8 (0.7%)	14 (1.3%)

a: p=0.010; b: p=0.124

Symptomatic VTE

Symptomatic VTE was analyzed based on the safety population in RECORD studies. The following table shows the rate of symptomatic VTE in RECORD 1 and 2 in patients undergoing THR surgery. There was a statistically significant difference in the symptomatic VTE rate between the two treatment groups in RECORD 2 trial only ($p<0.01$ using Fisher's exact test).

In the RECORD 2 trial, study patients in the enoxaparin control group received enoxaparin 40 mg once daily for 13 days followed by placebo for 23 days. When the symptomatic VTE rate was analyzed by enoxaparin control period and placebo control period separately, the symptomatic VTE rate was similar between the Rivaroxaban treatment and enoxaparin treatment during the enoxaparin control period ($p=0.19$ using Fisher's exact test) and lower with Rivaroxaban treatment than with placebo during the placebo control period ($p=0.02$ using Fisher's exact test). The difference in the symptomatic VTE rate between the two treatment groups was mainly due to more symptomatic proximal and distal DVT reported with placebo treatment.

Symptomatic VTE in Safety Population in THR Trials

	RECORD 1		RECORD 2	
Endpoint	Rivaroxaban 10mg qd N=2209	Enoxaparin 40mg qd N=2224	Rivaroxaban 10mg qd N=1228	Enoxaparin 40 mg qd + Placebo N=1229

Symptomatic VTE	6 (0.27%)	11 (0.49%)	3 (0.24%) E[a]: 1 (0.08%) P[b]: 2 (0.16%)	15 (1.22%) E: 4 (0.33%) P: 11 (0.90%)
Nonfatal PE	4 (0.18%)	1 (0.04%)	1 (0.08%) E: 0 P: 1 (0.08%)	4 (0.33%) E: 1 (0.08%) P: 3 (0.24%)
Fatal PE	0	1 (0.04%)	0 E: 0 P: 0	1 (0.08%) E: 1 (0.08%) P: 0
Proximal DVT	0	5 (0.22%)	1 (0.08%) E: 1 (0.1%) P: 0	9 (0.73%) E: 2 (0.16%) P: 7 (0.57%)
Distal DVT	3 (0.14%)	6 (0.27%)	1 (0.08%) E: 0 P: 1 (0.08%)	7 (0.57%) E: 2 (0.16%) P: 5 (0.41%)

a: E-enoxaparin control period
b: P-placebo control period

The following table shows the symptomatic VTE in RECORD 3 and 4 studies in patients undergoing TKR surgery. The symptomatic VTE rate was numerically lower with Rivaroxaban treatment as compared to enoxaparin treatment but the difference between the two treatment groups was statistically significant in RECORD 3 only ($p<0.05$ using Fisher's exact test). It was noted that more symptomatic proximal DVT events occurred in the Rivaroxaban group than in the enoxaparin control group in both RECORD 3 and 4 studies.

Symptomatic VTE in Safety Population in TKR Trials

	RECORD 3		**RECORD 4**	
Endpoint	Rivaroxaban 10mg qd N=1220	Enoxaparin 40mg qd N=1239	Rivaroxaban 10mg qd N=1526	Enoxaparin 30mg bid N=1508
Symptomatic VTE	8 (0.66%)	24 (1.94%)	11 (0.72%)	18 (1.19%)
Nonfatal PE	0	4 (0.32%)	5 (0.33%)	8 (0.53%)
Fatal PE	0	0	1 (0.06%)	0
Proximal DVT	3 (0.25%)	1 (0.08%)	5 (0.33%)	1 (0.07%)
Distal DVT	6 (0.50%)	20 (1.61%)	3 (0.20%)	9 (0.60%)

The following table shows the symptomatic VTE events reported during the follow-up period from RECORD studies. The rate was similar between the two treatment groups (0.16% vs. 0.19%). It was noted that there were more VTE events in the rivaroxaban group (5, 0.41%) than in the enoxaparin group (3, 0.24%) in RECORD 3 trial (11356). Overall, there were 7 PE and 2 proximal DVT and 1 distal DVT in the rivaroxaban group comparing 6 PE, 5 proximal DVT and 5 distal DVT in enoxaparin group.

Symptomatic VTE during the follow-up period in RECORD studies

	Rivaroxaban	Enoxaparin
SYMPTOMATIC VENOUS THROMBOEMBOLISM (FOLLOW-UP)		
ANY EVENT		
11354	1/ 2209 (0.05%)	4/ 2224 (0.18%)
11355	3/ 1526 (0.20%)	3/ 1508 (0.20%)
11356	5/ 1220 (0.41%)	3/ 1239 (0.24%)
11357	1/ 1228 (0.08%)	2/ 1229 (0.16%)
POOLED	10/ 6183 (0.16%)	12/ 6200 (0.19%)
PULMONARY EMBOLISM (FOLLOW-UP)		
11354	0/ 2209 (0.00%)	0/ 2224 (0.00%)
11355	3/ 1526 (0.20%)	2/ 1508 (0.13%)
11356	3/ 1220 (0.25%)	2/ 1239 (0.16%)
11357	1/ 1228 (0.08%)	2/ 1229 (0.16%)
POOLED	7/ 6183 (0.11%)	6/ 6200 (0.10%)
DEEP VEIN THROMBOSIS, PROXIMAL (FOLLOW-UP)		
11354	1/ 2209 (0.05%)	3/ 2224 (0.13%)
11355	0/ 1526 (0.00%)	1/ 1508 (0.07%)
11356	1/ 1220 (0.08%)	0/ 1239 (0.00%)
11357	0/ 1228 (0.00%)	1/ 1229 (0.08%)
POOLED	2/ 6183 (0.03%)	5/ 6200 (0.08%)
DEEP VEIN THROMBOSIS, DISTAL (FOLLOW-UP)		
11354	0/ 2209 (0.00%)	4/ 2224 (0.18%)
11355	0/ 1526 (0.00%)	0/ 1508 (0.00%)
11356	1/ 1220 (0.08%)	1/ 1239 (0.08%)
11357	0/ 1228 (0.00%)	0/ 1229 (0.00%)
POOLED	1/ 6183 (0.02%)	5/ 6200 (0.08%)

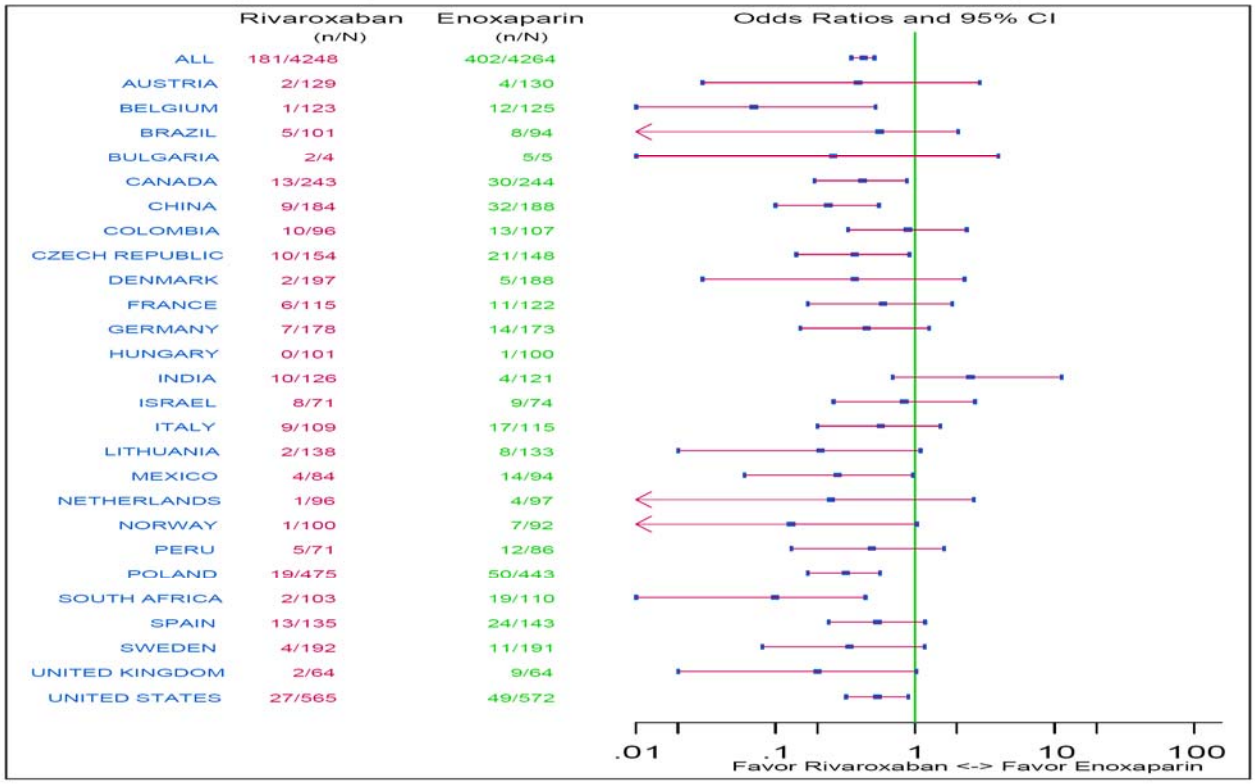
6.1.6 Other Endpoints

The sponsor performed additional efficacy analysis for composite endpoint of symptomatic VTE or death in RECORD studies. This composite endpoint is not a pre-specified endpoint for the efficacy analysis in the study protocol in RECORD studies.

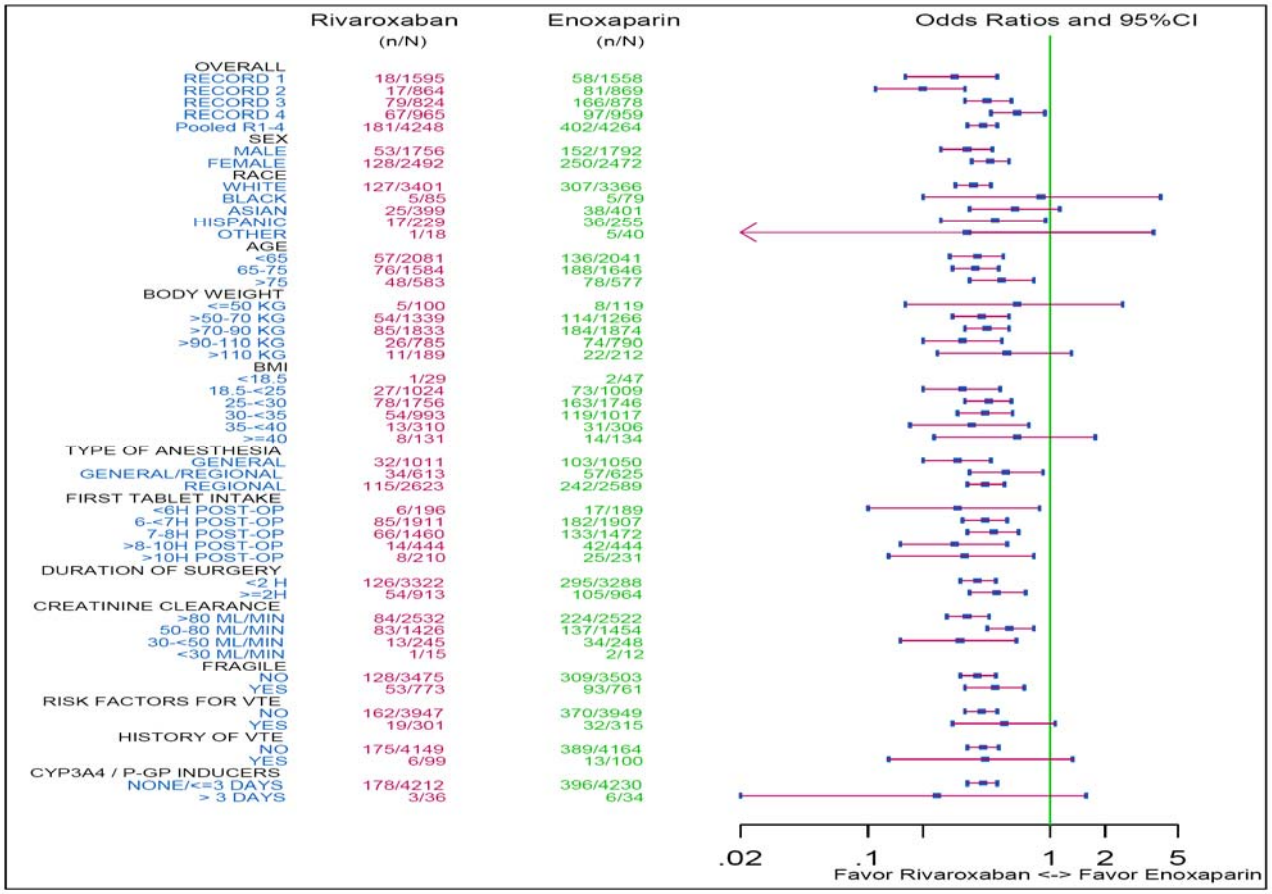
6.1.7 Subpopulations

The following Figure shows the total VTE and its odds ratio by country in pooled RECORD studies. The efficacy results were consistent with the primary efficacy analysis result in most countries except in India where enoxaparin showed better efficacy than Rivaroxaban treatment.

Figure 3-7: Total VTE and Corresponding Odds Ratio (95% CI) by Country (MITT Population of the Pooled RECORD 1-4 Studies)



The following figure shows the total VTE by treatment in subgroup analysis in pooled RECORD studies. The efficacy results were consistent with the primary efficacy analysis results in most subgroups except in black patients with no difference between the two treatment groups.



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose of Rivaroxaban (10 mg) was evaluated in phase 3 trials. The selection of Rivaroxaban 10 mg once daily dosing regimen in phase 3 trials was based on the efficacy and safety results from 4 phase 2 dose ranging studies.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No studies have been conducted to evaluate the persistence of efficacy and/or tolerance effects of Rivaroxaban treatment.

6.1.10 Additional Efficacy Issues/Analyses

The sponsor presented an analysis of a composite endpoint of symptomatic VTE or death as one efficacy endpoint for pooled RECORD studies in the submission. The sponsor seeks to use the pooled analysis to make a claim of superiority to enoxaparin for "symptomatic VTE or death" endpoint. This composite endpoint was not a pre-specified efficacy endpoint in the individual RECORD study protocols. This pooled analysis was not mentioned during the Special Protocol Assessment for RECORD protocols and was not a part of SPA agreement. However, the sponsor

indicated that it was pre-specified in the statistical analysis plan before unblinding the data. There are significant problems for pooling the four RECORD studies together due to the different treatment duration between the two treatment groups in RECORD 2 study (rivaroxaban for 35 days and enoxaparin for 12 days) and use of an unapproved dosing regimen of enoxaparin (40 mg once daily) in RECORD 4 study. Because of these limitations, pooling analysis is not appropriate. Therefore, the pooled analysis is not acceptable for establishing efficacy or claiming superiority as the sponsor proposes.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

All completed clinical studies and safety update from ongoing studies listed under Section 5.1 Table of Clinical Studies were used to evaluate the safety of Rivaroxaban. Some safety data from the ongoing studies are still blinded.

7.1.2 Adequacy of Data

The current safety database based on completed clinical studies is insufficient to evaluate hepatotoxicity of rivaroxaban. In completed clinical studies, 92% of study patients were exposed to <35 days of Rivaroxaban treatment and only 6% (635 patients) were exposed to Rivaroxaban for 3 months. Previous experience with product, EXANTA (ximelagatran), that causes drug-induced liver injury suggested short term tolerance does not necessarily predict long term safety (NDA 21-686, Medical Review, Dr. Ruyi He, M.D., 9/27/04; Cardiovascular and Renal Drug Advisory Committee Transcript, 9/10/04). In addition, enoxaparin, which is known to cause benign liver enzyme elevations and such elevations are fully reversible (NDA 20-164, Lovenox labeling), was used as control in all completed short-term Phase 3 clinical trials and that may confound the evaluation of hepatic signal in these trials. Therefore, long-term safety data with a different control that has not been shown to increase liver enzymes, such as Coumadin (warfarin), will be needed to fully evaluate the hepatotoxicity of rivaroxaban.

Furthermore, because rivaroxaban is an oral anticoagulant that doesn't require routine monitoring during treatment, off-label, long-term use could be widespread in clinical practice to replace current available oral product (coumadin) due to convenience, especially in atrial fibrillation population for stroke prevention and in patients who require long-term VTE

prophylaxis and treatment. The prevalence of atrial fibrillation in the United States has been projected to increase from 2 to 5 million in 2000 to 6 to 12 million in 2050 (Special Report, Prevention of Atrial Fibrillation, Report from a National Heart, Lung, and Blood Institute Workshop, *Circulation* 2009; 119:606-618). Therefore, thorough evaluation for hepatotoxicity and long-term safety in the long-term clinical trial is extremely important.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

Pooling data across studies to estimate and compare mortality, incidence of all SAEs, bleeding events, cardiovascular events, and hepatic events.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The following table summarizes the Rivaroxaban exposure in completed clinical studies. Among 10,600 patients who were exposed to Rivaroxaban in completed studies, 6183 were from phase 3 trials, 3300 were from phase 2 trials, and 1117 were from phase 1 trials. Among all exposed patients, 6095 (57.5%) were exposed to Rivaroxaban for ≤12 days, 3622 (34.2%) for 28-35 days, 203 (2%) between 36 and 12 weeks and 635 (6%) received rivaroxaban for at least 12 weeks.

Rivaroxaban Exposure in Completed Studies

Indication/Population	Rivaroxaban Dose	Duration (Mean±SD)	Number of patients
Phase 3 VTE prophylaxis			
RECORD 1-2 (THR)	10 mg once daily	33±7 days	3437
RECORD 3-4 (TKR)	10 mg once daily	12±3 days	2746
Phase 2 VTE prophylaxis	5, 10, 20, 30, 40 and 60mg total daily dose	8 days	2232
Phase 2 VTE treatment	20, 30, 40 and 60 mg total daily dose	78 (≥12 week)	883 (635)
Phase 2 Atrial Fibrillation (Japan)	5, 10, 15 , 20, 30, 40, and 60 mg total daily dose	28 days	185
Phase 1	variable	≤10 days	1117

Total		≤35 days (92%) ≥12 week (6%)	10,600

Drug exposure in RECORD studies

In the 4 RECORD studies, 6,183 subjects who were randomized to rivaroxaban and 6,200 who were randomized to enoxaparin comparator received at least 1 dose of blinded study medication (see table below). Eighty-six randomized subjects in the rivaroxaban group and 5 in the enoxaparin group never received active study medication due to the unbalanced start times of the treatments.

Number of subjects in the safety population of each RECORD study

Study	Rivaroxaban	Enoxaparin	Total
RECORD 1	2209	2224	4433
RECORD 2	1228	1229	2457
Total # hip subjects	**3437**	**3453**	**6890**
RECORD 3	1220	1239	2459
RECORD 4	1526	1508	3034
Total # knee subjects	**2746**	**2747**	**5493**
Grand Total	**6183**	**6200**	**12,383**

The following table shows the duration of treatment with active study drug in each of the RECORD studies. In the RECORD 2 study, after Day 12, active enoxaparin was discontinued and placebo was continued until Day 35.

Table 1-3: Duration of Treatment of Active Study Medication by Study (Mean Days ± SD) (Subjects Valid for Safety Analysis in RECORD Studies)

Study	Rivaroxaban	Enoxaparin
RECORD 1	33.4 ± 6.9	33.7 ± 8.2
RECORD 2	33.5 ± 6.9	12.4 ± 3.0
RECORD 3	11.9 ± 2.3	12.5 ± 3.0
RECORD 4	11.7 ± 2.5	11.0 ± 2.4

Demographics and Baseline Characteristics in RECORD Studies

The following table shows the demographic and baseline characteristics of the safety population in the combined 4 Phase 3 RECORD studies. Among the 12,383 subjects (6183 received Rivaroxaban, 6200 received enoxaparin) undergoing elective THR or TKR surgery, 4951 were men (40%) and 7432 (60%) were women, and 79% were White. Mean age of subjects was 64 years with 53% of subjects over 65 years and 15% of the subjects over 75 years. The mean BMI was 28.8 kg/m^2 with 36% of the subjects having a BMI >30 kg/m^2. Seven percent of the subjects had a calculated creatinine clearance <50 mL/min (moderate renal impairment) and 0.5% (35 in

the rivaroxaban group and 22 in the enoxaparin group) had a calculated creatinine clearance <30 mL/min (severe renal impairment). Medical history findings showed that 52% of subjects had hypertensive disorders, and 7% of subjects had upper or lower limb fractures/dislocations. Hepatic disease was reported in the medical history of 3% of subjects. This was mostly a history of gallbladder disease (1.7%) and hepatocellular damage/hepatitis (1.0%).

Compared with the combined 2 THR studies (RECORD 1 and 2), there were slightly more women, fewer Whites with greater mean age and weight in the combined 2 TKR studies (RECORD 3 and 4). There was a similar percentage of subjects with at least moderate or severe renal impairment, and hepatic disorder (2.7%-3.4%). There was a similar percentage of fragile subjects who were defined as those with age >75 years and/or body weight <50 kg and/or a calculated creatinine clearance <50 mL/min at baseline. There was a lower percentage of subjects in the THR studies with a history of hypertensive disorders (45%) than in the TKR studies (61%).

For the pooled RECORD 1-4 studies and for the separately pooled THR and TKR studies, demographic and baseline characteristics of subjects were well balanced in each of the 2 treatment groups, showing very similar characteristics to those of the respective total populations of each study pool. The medical history findings for the THR and TKR studies were similar for both treatment groups.

Demographics and Baseline Characteristics in Safety Population in RECORD 1-4 Studies

	Total for THR Studies (N=6890)	Total for TKR Studies (N=5493)	Total for All Studies (N=12383)
Sex N (%)			
Male	3110 (45%)	1841 (34%)	4951 (40%)
Female	3780 (55%)	3652 (66%)	7432 (60%)
Race N (%)			
Missing	230 (3%)	153 (3%)	383 (3%)
White	5687 (83%)	4037 (73%)	9724 (79%)
Black	103 (1%)	181 (3%)	284 (2%)
Asian	498 (7%)	736 (13%)	1234 (10%)
American Indian	3 (<1%)	5 (<1%)	8 (<1%)
Hispanic	329 (5%)	353 (6%)	682 (6%)
Uncodable	40 (1%)	28 (1%)	68 (1%)
Age (yrs.) Mean±SD	62.6 ±12.2	65.9 ±9.5	64.1 ±11.2
Age (categorized) N (%)			
<65 yrs	3532 (51%)	2288 (42%)	5820 (47%)
65-75 yrs	2460 (36%)	2275 (41%)	4735 (38%)
Weight (kg) Mean±SD	77.0 ±16.2	82.8 ±18.2	79.6 ±17.4
Weight (categorized) N (%)			
<=50 kg	228 (3%)	81 (1%)	309 (2%)

>50-70 kg	2405 (35%)	1367 (25%)	3772 (30%)
>70-90 kg	2956 (43%)	2445 (45%)	5401 (44%)
>90-110 kg	1091 (16%)	1159 (21%)	2250 (18%)
>110 kg	198 (3%)	435 (8%)	633 (5%)
Missing	12 (<1%)	6 (<1%)	18 (<1%)
BMI (kg/m^2) Mean±SD	27.5±4.9	30.3 ±5.6	28.8 ±5.4
BMI (categorized) N (%)			
<18.5	92 (1%)	17 (<1%)	109 (1%)
18.5 - <25	2091 (30%)	808 (15%)	2899 (23%)
25 - <30	2800 (41%)	2116 (39%)	4916 (40%)
30 - <40	1764 (26%)	2222 (40%)	3986 (32%)
>=40	123 (2%)	322 (6%)	445 (4%)
Missing	20 (<1%)	8 (<1%)	28 (<1%)
Creatinine clearance (ml/min) Mean±SD	90.2±30.9	91.6 ±33.2	90.8 ±32.0
Creatinine clearance (categorized) N (%)			
>80 ml/min	4015 (58%)	3200 (58%)	7215 (58%)
50-80 ml/min	2333 (34%)	1874 (34%)	4207 (34%)
30-<50 ml/min	447 (6%)	342 (6%)	789 (6%)
<30 ml/min	35 (1%)	22 (<1%)	57 (<1%)
missing	60 (1%)	55 (1%)	115 (1%)
Fragile subject[a] N (%)			
No	5633 (82%)	4360 (79%)	9993 (81%)
Yes	1257 (18%)	1133 (21%)	2390 (19%)

BMI=Body Mass Index, CL_{CR} = creatinine clearance
Note: Percentages are calculated including missing values.
[a] Fragile definition: Age >75 years and/or calculated creatinine clearance (CL_{CR}) <50 ml/min and/or weight ≤50 kg

Phase 2 studies

Demographic and baseline characteristics for subjects included in the 4 Phase 2 orthopedic VTE studies were similar and well balanced between the rivaroxaban and enoxaparin treatment groups. Approximately 98% of subjects in both treatment groups were white, and more than 58% were female. Approximately 15% of subjects in both treatment groups were more than 75 years of age, and mean BMI was approximately 28 kg/m2 in both treatment groups.

Demographics and Baseline Characteristics in safety population in VTE prophylaxis trials (Studies 10942, 10944, 10945, and 11527)

Characteristics	RIVA Total (N=2232)		ENOX Total (N=555)	
Sex, n (%)				
Male	896	(40.1%)	231	(41.6%)
Female	1336	(59.9%)	324	(58.4%)
Race, n (%)				
White	2184	(97.8%)	546	(98.4%)
Black	21	(0.9%)	3	(0.5%)
Asian	12	(0.5%)	2	(0.4%)
American Indian	3	(0.1%)	0	(0%)
Hispanic	8	(0.4%)	3	(0.5%)
Uncoded	4	(0.2%)	1	(0.2%)
Age (years)				
Mean	65.3		65.2	
Median	66.0		66.0	
Range	26.0 – 93.0		27.0 – 92.0	
Age (categorized), n (%)				
< 65 years	1000	(44.8%)	231	(41.6%)
65 – 75 years	878	(39.3%)	238	(42.9%)
> 75 years	354	(15.9%)	86	(15.5%)
Weight (kg)				
Mean	79.9		79.4	
Median	79.0		79.2	
Range	45.0 – 173.0		45.5 – 145.0	
Body mass index (kg/m^2)				
Mean	28.6		28.5	
Median	27.8		28.1	
Range	17.2 – 61.3		15.9 – 51.6	
BMI (categorized), n (%)				
<18.5 (kg/m^2)	16	(0.7%)	8	(1.4%)
18.5 - <25 (kg/m^2)	540	(24.2%)	131	(23.6%)
25 - <30 (kg/m^2)	937	(42.0%)	226	(40.7%)
30 - <40 (kg/m^2)	665	(29.8%)	176	(31.7%)
≥40 (kg/m^2)	74	(3.3%)	14	(2.5%)

Key: BMI = body mass index; ENOX = enoxaparin; RIVA = rivaroxaban
Source: Table 11-2 in MRR-00300 5.3.5.3.3-17

Demographic and baseline characteristics for subjects included in the 2 Phase 2 DVT treatment studies were similar and well balanced between the 2 treatment groups. Approximately 92% of subjects in both groups were white, and more than 55% of subjects in each group were male. In Study 11223, a prior history of DVT was the most common thromboembolism risk factor, occurring in 108 (18%) of all subjects in the safety population.

Demographics and Baseline Characteristics in safety population in DVT treatment trials (Studies 11223 and 11528)

Characteristics	Rivaroxaban Total (N=883)		Heparin/VKA Total (N=263)	
Sex, n (%)				
Male	495	(56.1%)	150	(57.0%)
Female	388	(43.9%)	113	(43.0%)
Race				
White	818	(92.6%)	243	(92.4%)
Black	28	(3.2%)	12	(4.6%)
Asian	4	(0.5%)	1	(0.4%)
American Indian	1	(0.1%)	0	(0%)
Hispanic	28	(3.2%)	7	(2.7%)
Uncoded	4	(0.5%)	0	(0%)
Age (years)				
Mean	58.8		57.7	
Median	61.0		59.0	
Range	18.0 – 94.0		21.0 – 92.0	
Age (categorized), n (%)				
< 65 years	520	(58.9%)	151	(57.4%)
65 – 75 years	208	(23.6%)	60	(22.8%)
> 75 years	155	(17.6%)	52	(19.8%)
Weight (kg)				
Mean	80.2		81.1	
Median	79.0		80.0	
Range	37.0 - 209.0		41.0 – 138.0	
BMI (kg/m^2)				
Mean	27.5		27.7	
Median	26.9		26.8	
Range	13.8 – 56.7		18.2 – 44.4	
BMI (categorized), n (%)				
<18.5 (kg/m^2)	40	(4.5%)	6	(2.3%)
18.5 - <25 (kg/m^2)	273	(30.9%)	84	(31.9%)
25 - <30 (kg/m^2)	343	(38.8%)	97	(36.9%)
30 - <40 (kg/m^2)	204	(23.1%)	72	(27.4%)
≥40 (kg/m^2)	23	(2.6%)	4	(1.5%)

Key: BMI = body mass index; LMW = low molecular weight; VKA = vitamin K antagonist

Three phase 2 atrial fibrillation studies were conducted in Japan. Study 11390 was an open-label, uncontrolled, sequential dose panel study, while Studies 11866 and 12024 were randomized, open-label, warfarin-controlled, parallel-group, dose-range studies (5 to 20 mg daily doses for 28 days). The age ranges of rivaroxaban subjects in Studies 11390, 11866, and 12024 were 34-81 years, 45-85 years, and 30-92 years, respectively. Approximately 94%, 80%, and 76%, respectively of all rivaroxaban subjects were male. Demographic and baseline characteristics for subjects included in warfarin-controlled studies were similar and well balanced between the treatments groups except more males in the warfarin group in Study 12024.

7.2.2 Explorations for Dose Response

Four phase 2 trials were conducted to explore the dose response relationship and all 4 studies showed an increased risk of bleeding events with increasing rivaroxaban dose. Total daily doses

from 5 to 20 mg were considered to be similar to the comparator, enoxaparin, while doses over 20 mg had increased rates of bleeding events. Only one dose of rivaroxaban (10 mg daily) was studied in all phase 3 trials.

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

Liver function tests, routine hematology and clinical chemistry including renal function (creatinine and urea) were measured during the clinical trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Phase 1 clinical pharmacokinetic studies were conducted to study the metabolism and clearance of rivaroxaban. Seventeen drug-drug interaction studies were conducted and showed that strong inhibitors of both metabolism (i.e., CYP3A4) and active secretion (i.e., P-glycoprotein [P-gp] and breast cancer resistance protein [Bcrp]) may result in a clinically relevant increased systemic exposure of rivaroxaban. (See Clinical Pharmacology review)

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Bleeding events were evaluated in phase 3 trials and the results are included under Section 7.3.4.1 Bleeding events.

7.3 Major Safety Results

7.3.1 Deaths

RECORD Studies

There were 13 (0.2%) and 25 (0.4%) deaths reported in the safety populations of rivaroxaban and enoxaparin, respectively, during the treatment (8 rivaroxaban and 15 enoxaparin) and follow-up (5 rivaroxaban and 10 enoxaparin) period in 4 RECORD studies.

This following table shows the number of deaths during the treatment and the follow-up period in each individual RECORD study. In RECORD 1 and 4 studies, the number of deaths was the same between the two treatment groups. In RECORD 2 and 3 studies, there were few deaths with rivaroxaban than with enoxaparin. This may have been related to a short treatment duration of enoxaparin in RECORD 2 study and unapproved enoxaparin dose used in the control in the RECORD 3 study. In RECORD 2 study, 3 deaths occurred during enoxaparin treatment period, 3 occurred in placebo treatment period and 2 occurred during the follow-up.

Deaths in RECORD Studies

RECORD	Rivaroxaban	Enoxaparin or Enoxaparin/placebo
1 (hip)	5/2209 (0.2%)	5/2224 (0.2%)
2 (hip)	2/1228 (0.2%)	8/1229 (0.7%) (Enoxaparin/placebo)
3 (knee)	0/1220 (0.0%)	6/1239 (0.5%) (40 mg od)
4 (knee)	6/1526 (0.4%)	6/1508 (0.4%)

One subject (RECORD 2 Subject 11357-120037004) was randomized to rivaroxaban but did not receive any study medication and was not counted as an event in the safety population.

One subject in the rivaroxaban group (11354-160084031) and one subject in the enoxaparin group (11355-90002-25006, not included in the table below) did not receive active study treatment but received placebo treatment and was included in the safety population.

Two subjects randomized to rivaroxaban died of fatal bleeding. One did receive study drug (placebo enoxaparin) prior to surgery but did not receive active rivaroxaban treatment after surgery. Another rivaroxaban subject died of an upper gastrointestinal bleed on Day 6 of the study.

There were 1 and 3 deaths on rivaroxaban and enoxaparin, respectively, that were adjudicated as VTE-related. However, the causes of death from case report forms mentioned pulmonary embolism in 3 deaths with rivaroxaban and in 6 deaths with enoxaparin.

There were 7 and 12 deaths adjudicated as cardiovascular deaths on rivaroxaban and enoxaparin, respectively.

There were no hepatic disorder deaths observed in the RECORD studies.

The following Table lists the investigator-reported causes of death for each subject who died.

Deaths in RECORD Studies

Study Medication Study-Subject Number	Age	Race	Sex	Date of Last ASM	Day of Death Relative to ASM Start	Cause of Death (from case report form)
Rivaroxaban 10 mg od						
11354-160084031	74	NA	F	Subject did not receive active study medication		Hemorrhage which led to collapse; disseminated intravascular coagulation syndrome
11354-300014007	85	White	F	35	(b) (6)	Septic shock with multiorgan failure
11354-180214015	70	White	F	8		Adenocarcinoma of the stomach
11354-520014023	81	White	M	2		Suspected pulmonary embolism
11354-240204007	77	White	M	10		Suspected massive pulmonary thromboembolism
11357-500087008	57	White	F	34		Acute respiratory failure
11357-500107008	91	White	F	1		Respiratory insufficiency; shock; hypovolemic post-hip arthroplasty
11357-120037004*	70	White	M	Subject did not receive any study medication		Multiple injuries
11355-260195005	83	White	F	2	(b) (6)	Acute interstitial pneumonia
11355-600095029	71	Asian	M	10		Natural death
11355-140105153	53	White	M	6		Upper gastrointestinal bleed
11355-140165070	79	White	F	4		Sepsis
11355-140235019	80	White	F	2		Cardiopulmonary arrest, cardiac arrest x 2, pulmonary embolism
11355-140495008	69	White	F	3		Aspiration pneumonia; pulmonary edema; respiratory failure
Enoxaparin 40 mg od						
11354--280074017	78	White	F	1		Postanemic coma after cardiac arrest and cardiopulmonary reanimation
11354-180104005	46	White	M	4		Pulmonary embolism
11354-370124003	73	NA	F	4		Multiorgan failure
11354-470034006	46	White	F	16		Sepsis
11354-470034009	87	White	F	18		Cardiac arrest
11357-500027004	84	White	F	3		Unexpected bleeding; blood polytransfusion; SIRS/SARA; septic shock; death
11357-500027009	76	White	F	13		Massive pulmonary embolism after prosthetic right hip dislocation
11357-540067004	75	Asian	F	1		Fat embolus syndrome
11357-480027027	81	Hispanic	F	11		Septic shock
11357-320057006	86	White	F	11		Respiratory failure
11357-320057017	83	White	F	4		Bronchoaspiration
11357-320057018	74	White	M	7		Acute abdominal distention; elevated transaminases; renal failure; intestinal palsy
11357-370087001	69	White	F	10		Pulmonary embolism
11356-280166007	75	White	M	14		Suspected pulmonary embolism
11356-540156016	76	Asian	M	5		Acute myocardial infarction
11356-100116011	79	White	M	14		Pneumonia
11356-640036002	75	Hispanic	M	13		Respiratory failure Type I-II
11356-370056011	77	White	F	11		Unknown; likely an acute myocardial infarction or acute pulmonary embolism
11356-370106019	67	White	M	15		Pulmonary embolism
Enoxaparin 30 mg bid						
11355-600075027	79	Asian	M	6		Cardiac arrest
11355-600105007	67	Asian	F	6		Myocardial infarction
11355-600105031	78	Asian	M	6		Septicemia
11355-320075009	86	Hispanic	F	4		Pneumonia and septic shock
11355-140045010	72	White	M	10		Metastatic cancer

* Subject received no study medication and was not included in the safety population.
Key: ASM = active study medication; F = female; M = male; NA = not available; SIRS = systemic inflammatory response syndrome; SARA = sexually acquired reactive arthritis
Source: Table 14.3.2/1 in Study RECORD 1 (MRR-00233), Study RECORD 2 (MRR-00234); Study RECORD 3 (MRR-00218); and Study RECORD 4 (MRR-A41857).

Phase 2 and Phase 1 Studies

In the orthopedic VTE prophylaxis studies a total of 8 (0.4%) deaths were observed in the pooled rivaroxaban arm compared with 0 (0%) deaths in the pooled enoxaparin arm. There were 4-fold more subjects exposed to rivaroxaban compared with enoxaparin. The causes of death for 7

deaths in Rivaroxaban are listed in the table below. Three of them died of PE. One death in the rivaroxaban group, not included in the table below, occurred approximately 4 months after the last dose of study medication. The subject (10944-84008) received rivaroxaban 10 mg twice daily for 8 days and developed liver failure 39 days after the end of treatment and subsequently died. This case will be discussed further in hepatic event section.

Deaths in VTE prophylaxis Phase 2 trials
(Subjects in Studies 10942, 10944, 10945, and 11527)

Treatment Subject	Sex	Race	Age	Cause of Death	Day of Death[a]
RIVA 2.5 mg bid					(b) (6)
10942-63-034	F	White	76	Sudden death, cardiac arrest, pulmonary embolism	
10945-009-009006	M	White	79	Shortness of breath Pulmonary edema Respiratory failure Acute respiratory distress	
10945-129-129010	F	White	71	Pulmonary embolism	
RIVA 5 mg bid					
10944-31-014	F	White	81	Sepsis, pneumonia	
RIVA 10 mg bid					
10944-79-005	M	White	93	Bronchopneumonia	
10945-010-010040	F	White	75	Pulmonary embolism	
RIVA 30 mg od					
10942-46-024	M	White	80	Cardiorespiratory arrest	

[a] Day of death relative to the day of last dose of study treatment (source of relative dates for death and dosing information is the narrative summary for each subject).
Key: bid = twice daily; od = once daily; RIVA = rivaroxaban
Source: Subject narratives in Study 10942 (MRR-00086); Study 10944 (MRR-00135); Study 10945 (MRR-00161); and Study 11527 (MRR-00174).

In the DVT treatment studies, a total of 30 (3.4%, n=883) rivaroxaban subjects and 6 (2.3%, n=263) comparator subjects, died either during or after study treatment. The causes of deaths assessed by the investigators are listed in the Table below. Among 30 deaths in the Rivaroxaban subjects, the cause of death was considered to be cancer in 12 subjects, infection in 4 subjects, sudden death in 2 subjects, PE in 1 subject, bleeding in 1 subject, and liver failure in 1 subject. The subject (11223-506006) who died of liver failure will be further discussed in hepatic event section. Among 6 deaths in enoxaparin subjects, 2 each died of cancer and bleeding, and 1 each died of PE and infection.

Deaths in DVT treatment Trials
(Subjects in Studies 11223 and 11528)

Treatment Subject	Sex	Race	Age	Cause of Death[a]	Day of Death[b]
RIVA 10 mg bid					(b) (6)
11223-505007	F	White	82	Unknown	
11223-378002	F	Hispanic	62	Lung adenocarcinoma Pulmonary embolism (acute) Respiratory failure	
11223-356001	M	White	71	Graft infection	
11223-759001	M	White	77	Septic shock Acute respiratory distress syndrome Renal failure	
11223-702001	M	White	71	Acute multiple organ failure due to disseminated intravascular coagulation	
RIVA 20 mg od					
11528-552003	F	White	63	Unknown	
11528-553009	M	White	78	Gastric cancer	
11528-503004	F	White	76	Myocardial infarction	
11528-253003	M	White	74	Cardiorespiratory arrest	
RIVA 30 mg od					
11528-551003	F	White	76	Lower GI bleeding	
11528-554001	M	Black	67	Pulmonary embolism	
11528-351010	F	White	75	Pancreatic cancer	
11528-301003	M	White	52	Unknown	
11528-51002	M	White	59	Lung metastases	
11528-52009	F	Asian	56	Complications of pancreatic cancer	
11528-57004	M	White	41	Injury (car accident)	
11528-204003	M	White	56	Colon cancer	
11528-103003	F	White	79	Sudden death	
RIVA 20 mg bid					
11223-304004	F	White	68	Multiorgan failure; metastatic carcinoma	
11223-306002	F	White	34	Metastatic adenocarcinoma of cervix	
11223-651001	M	White	77	Pneumonia	
11223-402004	M	White	68	Lung carcinoma	
RIVA 40 mg od					
11223-506006	F	White	72	Hepatitis B; liver failure	
11223-252007	M	White	79	Sudden cardiac death	
11528-306008	M	White	74	Pulmonary edema	
11528-308001	F	White	52	Metastatic cancer of cervix	
11528-51011	F	White	47	Renal cell adenocarcinoma	
11528-151003	F	Black	51	Renal failure	
RIVA 30 mg bid					
11223-278001	M	Hispanic	50	Cancer	
11223-603005	M	White	69	Dyspnea; metastatic adenocarcinoma	
Comparator					
11223-378001	M	Hispanic	77	Sepsis	
11528-552008	M	White	78	Hemorrhagic stroke	
11528-312002	M	White	86	Pulmonary embolism; metastatic pancreatic tumor; liver metastases	
11528-51003	M	White	61	Prostate carcinoma	
11528-51007	F	White	62	Recurrent rectal hemorrhage	
11528-59001	M	White	75	Advanced bladder cancer	

[a] Cause of death reflects that reported by the investigator on the CRF. If no reason for death was listed on the CRF, adverse events with outcomes of death are listed.
[b] Day of death is relative to the day of last dose of study treatment.
Key: bid = twice daily; od = once daily; RIVA = rivaroxaban
Source: Table 14.3.2/1in Study 11223 (MRR-00150) and Study 11528 (MRR-00223)

No deaths were reported in the phase 2 atrial fibrillation studies (Japan), or in the Phase 1 studies.

7.3.2 Nonfatal Serious Adverse Events

RECORD Studies

The overall percentage of serious treatment-emergent adverse events was 6.6% in the

rivaroxaban group and 8.5% in the enoxaparin group. The following table presents the incidence of serious treatment-emergent adverse events that occurred at ≥0.1% in descending order of frequency, based on events on rivaroxaban.

The adverse events that were higher with rivaroxaban compared to enoxaparin were ALT increased, wound infection, femur fracture, operative hemorrhage, wound secretion, anemia, post-operative wound infection, acute renal failure, device related infection, hemorrhage, and nausea.

Incidence of the Serious Treatment-emergent Adverse Event that Occurred at ≥0.10% in the Rivaroxaban-treated Patients in Pooled RECORD 1-4 Studies

Preferred Term	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
ANY EVENT	**406 (6.57%)**	**528 (8.52%)**
Deep vein thrombosis	41 (0.66%)	110 (1.77%)
Alanine aminotransferase (ALT) increased	17 (0.27%)	11 (0.18%)
Dislocation joint prosthesis	14 (0.23%)	28 (0.45%)
Wound infection	14 (0.23%)	9 (0.15%)
Femur fracture	13 (0.21%)	6 (0.10%)
Pulmonary embolism	12 (0.19%)	22 (0.35%)
Joint dislocation	11 (0.18%)	24 (0.39%)
Operative hemorrhage	11 (0.18%)	7 (0.11%)
Hematoma	10 (0.16%)	10 (0.16%)
Wound secretion	10 (0.16%)	7 (0.11%)
Atrial fibrillation	9 (0.15%)	11 (0.18%)
Anemia	9 (0.15%)	5 (0.08%)
Hemoglobin decreased	8 (0.13%)	11 (0.18%)
Post operative wound infection	8 (0.13%)	7 (0.11%)
Myocardial infarction	6 (0.10%)	11 (0.18%)
Hepatic enzyme increased	6 (0.10%)	7 (0.11%)
Acute renal failure	6 (0.10%)	5 (0.08%)
Device related infection	6 (0.10%)	2 (0.03%)
Hemorrhage	6 (0.10%)	1 (0.02%)
Nausea	6 (0.10%)	1 (0.02%)

Phase 2 and Phase 1 Studies

In the orthopedic VTE prophylaxis studies, a total of 237 (11%) of subjects in the total rivaroxaban and 58 (10%) subjects in the total enoxaparin treatment groups reported serious adverse events. The incidence of treatment-emergent serious adverse events was higher at higher total daily doses of rivaroxaban due to the bleeding events of operative hemorrhage and hematoma. The most commonly-reported adverse events occurring at an incidence of >5% in the total rivaroxaban group were constipation (10% vs. 9%), nausea (16% vs. 19%), vomiting (11% vs. 12%), pyrexia (9% vs. 8%), anemia (7.2% vs. 6.8%), wound secretion (6% vs. 4.1%), decreased hemoglobin (5.4% vs. 4.9%), dizziness (5.3% vs. 5.6%), insomnia (6.6% vs. 7.9%),

DVT (7.6% vs. 11.9%), and hematoma (5.8% vs. 4%) in rivaroxaban and enoxaparin subjects, respectively.

In the Phase 2 DVT treatment studies, a total of 117 (13.3%) rivaroxaban subjects and 38 (14.4%) comparator subjects reported serious treatment-emergent adverse events. Among rivaroxaban subjects, the incidence of serious adverse events among dose groups did not suggest a dose-relationship.

In the Atrial Fibrillation Studies, in Study 11866, 1 rivaroxaban subject, and in Study 12024, 2 rivaroxaban subjects and 1 warfarin experienced treatment-emergent serious adverse events. In the Phase 1 studies, serious adverse events were reported by 8 subjects in 7 studies.

7.3.3 Dropouts and/or Discontinuations

The overall percentage of adverse events that led to discontinuation was 3.7% in the rivaroxaban group and 4.7% in the enoxaparin group. The following table presents the incidence of frequently-occurring adverse event that resulted in permanent discontinuation in descending order of frequency. The adverse events leading to permanent discontinuation were higher with rivaroxaban compared to enoxaparin were hematuria, angina pectoris, upper abdominal pain, tachycardia, anesthetic complication, vomiting, peripheral edema, and acute myocardial infarction.

AEs Leading to Permanent Discontinuation of Study Drug in RECORD 1-4 Studies

Preferred Term	Rivaroxaban (N=6183)	Enoxaparin (N=6200)
ANY EVENT	230 (3.72%)	288 (4.65%)
DVT	20 (0.32%)	39 (0.63%)
PE	11 (0.18%)	23 (0.37%)
Nausea	7 (0.11%)	13 (0.21%)
ALT increased	7 (0.11%)	7 (0.11%)
Vomiting	6 (0.10%)	5 (0.08%)
Atrial fibrillation	5 (0.08%)	12 (0.19%)
Operative hemorrhage	5 (0.08%)	9 (0.15%)
Myocardial infarction	5 (0.08%)	6 (0.10%)
Peripheral edema	5 (0.08%)	4 (0.06%)
Hematuria	5 (0.08%)	0 (0.00%)
Acute myocardial infarction	4 (0.06%)	3 (0.05%)
Angina pectoris	4 (0.06%)	1 (0.02%)
Tachycardia	4 (0.06%)	2 (0.03%)
Upper abdominal pain	4 (0.06%)	1 (0.02%)
Anesthetic complication	4 (0.06%)	2 (0.03%)

7.3.4 Significant Adverse Events

7.3.4.1 Bleeding Events

Major Bleeding

The following table shows the treatment-emergent major bleeding and its components in the pooled RECORD studies. The treatment-emergent bleeding events were those that occurred after double-blind administration of first study drug and no later than 2 days after the last intake of study drug. There were a total of 24 (0.4%) and 13 (0.2%) adjudicated treatment-emergent major bleeding events in the rivaroxaban and enoxaparin groups, respectively, with a study-stratified hazard ratio of 1.8 (95% CI: 0.9 to 3.6, p=0.076).

The incidence of major bleeding rate was relatively higher in the TKR patients (0.62% with rivaroxaban and 0.36% with enoxaparin) compared to the THR patients (0.20% with rivaroxaban and 0.09% with enoxaparin). The incidence of major bleeding was higher with rivaroxaban compared to enoxaparin in all RECORD studies except RECORD 2 study (0.27% and 0.09% in RECORD 1, 0.08% and 0.08% in RECORD 2, 0.57% and 0.48% in RECORD 3, and 0.39% and 0.21% in RECORD 4 for rivaroxaban and enoxaparin, respectively).

Major Bleeding Events in RECORD 1-4

	THR: RECORD 1-2		**TKR: RECORD 3-4**		**Overall**	
Bleeding Events	Rivaroxaban N=3437	Enoxaparin N=3453	Rivaroxaban N=2746	Enoxaparin N=2747	Rivaroxaban N=6183	Enoxaparin N=6200
Major Bleeding	7 (0.20%)	3 (0.09%)	17 (0.62%)	10 (0.36%)	24 (0.39%)*	13 (0.21%)
-Fatal bleeding	1 (0.03%)	0	1 (0.04%)	0	2 (0.03%)	0
-Bleeding into a critical organ	1 (0.03%)	1 (0.03%)	2 (0.07%)	4 (0.15 %)	3 (0.05%)	5 (0.08 %)
-Bleeding that required re-operation	2 (0.06%)	1 (0.03%)	10 (0.36%)	6 (0.22%)	12 (0.19%)	7 (0.11%)
-Clinically overt extrasurgical site bleeding associated with a >2 g/dL decrease in Hb	3 (0.09%)	1 (0.03%)	5 (0.18%)	0	8 (0.13%)	1 (0.02%)
-Clinically overt extrasurgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.09%)	1 (0.03%)	5 (0.18%)	0	8 (0.13%)	1 (0.02%)

*p=0.076

There were 2 fatal bleeding events reported in the rivaroxaban group as compared to none in the enoxaparin group.

One of the fatal bleeding events occurred in a subject (11354-160084031) who was randomized to study drug in RECORD 1 study but experienced a fatal bleed prior to receiving active rivaroxaban. The subject entered the study on 02 Oct 2006 and received placebo injection prior surgery at (b) (6) the subject underwent total hip replacement. He experienced hemorrhage at surgical site and urogenital hemorrhage. About 1

hour after surgery, his condition worsened and he was intubated. The subject received 9 transfusions with packed cells (1 x autologous, 8 x donor blood), a total of 3577 mL, within 7½ hours on the day of surgery. Despite new transfusions, the subject experienced hemolysis and "cardiovascular collapse", secondary to massive transfusion required due to severe hemorrhage. Disseminated intravascular coagulation (DIC) syndrome was suspected. Despite treatment with transfusion and adrenalin, ephedrine and dopamine for cardiovascular collapse (shock), and cardiac massage for resuscitation, the subject died on (b) (6) from hemorrhage at surgical site, urogenital hemorrhage and finally from cardiovascular shock.

The second fatal bleed occurred in a subject (11355-14010-5153) undergoing TKR surgery in RECORD 4 study. This 53 year old American male was randomized to receive rivaroxaban. On (b) (6), the subject underwent primary right knee arthroplasty under general anesthesia. He started Rivaroxaban on (b) (6). Intra-operative blood loss was 50 mL and an autotransfusion system was not used. A wound drain was present, and the subject had 140 mL and 30 mL of bloody drainage on (b) (6) and (b) (6), respectively. The subject was discharged from the hospital on (b) (6). The subject received Daypro® (oxaprozin) 1200 mg (b) (6)), Aleve® (naproxen) dose unspecified (b) (6) and Goody's Powder® (aspirin, caffeine, acetaminophen) 3 packets (b) (6) to (b) (6) for osteoporosis knee pain. (b) (6), the subject experienced tachycardia (The time was unspecified in the CRF). This adverse event was assessed as non-serious and unrelated to study drug. It remained unchanged with no action taken. On (b) (6) the subject presented to the emergency room with acute onset of hematemesis and melena associated with upper abdominal discomfort. Upper gastrointestinal endoscopy revealed massive upper gastrointestinal hemorrhage (felt to be likely secondary to nonsteroidal, anti-inflammatory drug), ulcer, and suboptimal visualization of the gastric lumen due to a large amount of retained blood and clots. He was transfused with of 250 mL x5 of donor packed cells. His oxygen saturation reportedly dropped into the mid 80's; he was intubated, became unresponsive, and a code was called unsuccessfully. Autopsy on (b) (6) revealed multiple benign gastric ulcers with no evidence of gastric perforation, 40 % stenosis of the circumflex coronary artery, mild aortic atherosclerosis, and hepatomegaly (2450 grams due to passive congestion). The investigator considered the event as related to the study drug. The Bleeding Adjudication Committee assessed the upper gastrointestinal bleed as constituting major bleeding.

Critical organ bleeding events occurred in 3 rivaroxaban subjects (retinal hemorrhage, adrenal hemorrhage, and post-procedural hematoma). The "post-procedural hematoma" was a subject experiencing a spinal hematoma before the start of active rivaroxaban. Critical organ bleeding events occurred in 5 enoxaparin subjects (catheter-site hemorrhage, subdural hemorrhage, extradural hematoma, catheter-related complication, and spinal epidural hemorrhage). The subject with a "catheter-site hemorrhage" had fluid in the epidural catheter that was blood-tinged. The subject with a "catheter-site complication" had a traumatic puncture during an epidural catheter insertion.

Most of the bleeding events in both groups were those that required re-operation (12 [0.19%] in the rivaroxaban group and 7 [0.11%] in the enoxaparin group).

More patients experienced clinically-overt extrasurgical site bleeding events that were associated with a decrease in hemoglobin or required a blood transfusion in the rivaroxaban group as compared to the enoxaparin group. There were 8 subjects on rivaroxaban and 1 subject on enoxaparin who experienced a clinically-overt extrasurgical site bleeding associated with a decrease of >2 g/dL in hemoglobin. These same subjects on rivaroxaban and enoxaparin also required blood transfusions. All of these events were gastrointestinal tract bleeding events.

The following table presents centrally adjudicated major bleeding events for individual subjects in the 4 RECORD studies. The bleeding events include major treatment-emergent bleeding events and those that occurred more than 2 days after the last intake of study medication. Four subjects in the rivaroxaban group (2 hematomas [4 and 24 days after the last dose, respectively], 1 hemarthrosis [25 days after the last dose), and a catheter site hemorrhage [prior to treatment]) and 4 subjects in the enoxaparin group (2 GI bleeding [6 days after the last dose in both] hematoma [18 days after the last dose], hemarthrosis [4 days after the last dose]) had major bleeding events more than 2 days after last intake of study medication, and these subjects are noted in the table with asterisks. One subject in the Rivaroxaban group experienced adrenal hemorrhage on Day 8 and later developed left frontal lobe infarct 8 days after the last dose of Rivaroxaban which transformed into hemorrhagic stroke in 2 weeks.

Major Bleeding Events (Central Adjudication) in RECORD 1-4 studies

Study Medication Study-Subject Number	Age	Sex	Adverse Event (MedDRA Preferred Term)	Date of Last ASM	Day of Bleeding Relative to ASM Start	Outcome
Rivaroxaban 10 mg od						
11354-100104016	67	M	Hematoma evacuation	34	(b) (6)	Resolved
11354-160084031	74	F	Hemorrhage	Subject did not receive active study drug		Death
11354-180154011	78	F	Gastrointestinal hemorrhage; hematemesis	3	(b) (6)	Resolved
11354-220014003	51	M	Retinal hemorrhage	40		Improved
11354-240054006	66	M	Gastrointestinal hemorrhage	35		Resolved
11354-350024032	64	M	Wound hemorrhage	31		Resolved
11357-120037006	54	F	Hematemesis; hemorrhagic diarrhea	17		Improved
11356-160016021	65	M	Operative hemorrhage	15		Resolved
11356-240036002	65	M	Post-procedural hemorrhage	14		Resolved
11356-240036020	78	F	Post-procedural hematoma	Subject did not receive active study drug		Resolved
11356-300026006*	49	M	Hematoma	13	(b) (6)	Resolved
11356-300026031	67	M	Hematoma	14		Resolved
11356-370056009	67	M	Rectal hemorrhage	13		Resolved
11356-370106010	54	M	Hemorrhage	14		Resolved
11356-370106022	60	M	Hemarthrosis	14		Resolved
11355-140045071*	80	F	Adrenal hemorrhage	8		Resolved
			Hemorrhagic stroke	8		Resolved
11355-140105018*	56	F	Subcutaneous hematoma	11		Resolved
11355-140105153	53	M	Upper GI hemorrhage	6		Death
11355-140115004	78	F	Hemarthrosis	11		Resolved
11355-140115016	69	F	Hematemesis	2		Resolved
11355-140205041*	69	F	Hemarthrosis	3		Resolved
11355-140225061	68	M	Incision site hemorrhage	1		Resolved
11355-140455077	59	M	Post-procedural hematoma	4		Resolved
11355-140705004	47	M	Hematoma	5		Resolved
11355-260135015	76	M	Gastrointestinal hemorrhage	2		Resolved
11355-350065008	63	F	Hemarthrosis	9		Resolved
11355-600015092*	60	M	Catheter site hemorrhage	12		Resolved
11355-900015002	71	F	Gastroduodenal hemorrhage	7		Resolved
Enoxaparin 40 mg od						
11354-100024030	69	M	Arterial hemorrhage	9		Resolved
11354-180214023*	78	F	Feces discolored	7		Resolved
11354-260054017	76	M	Gastrointestinal hemorrhage	14		Resolved
11357-340017005	78	F	Spinal epidural hemorrhage	1		Resolved
11356-100056012*	65	M	Subcutaneous hematoma	10		Resolved
11356-100106003	74	F	Extradural hematoma	2		Resolved
11356-180036023	74	F	Post-procedural hemorrhage	11		Resolved
11356-180106016	77	F	Catheter-related complication	11		Resolved
11356-300026018	81	M	Hematoma	6		Resolved
11356-350016024	81	M	Post-procedural hemorrhage	12		Resolved
11356-370106015	71	F	Wound hemorrhage	14		Resolved
11356-440046019*	74	M	Hemarthrosis	5		Resolved
Enoxaparin 30 mg bid						
11355-140105112	47	F	Subcutaneous hematoma	12		Resolved
11355-320075009*	86	F	Gastrointestinal hemorrhage	4		Resolved
11355-600015098	66	F	Catheter site hemorrhage	11		Resolved
11355-600105031	78	M	Subdural hemorrhage	6		Improved

Key: ASM = active study medication; F = female; GI = gastrointestinal; M = male; MedDRA = Medical Dictionary of Regulatory Activities

Source: Table 14.3.2/5 in Study RECORD 1 (MRR-00233), Study RECORD 2 (MRR-00234); Study RECORD 3 (MRR-00218); and Study RECORD 4 (MRR-A41857).

* Bleeding events for these subjects were not treatment emergent.

Note: Subject 11355-140045071 had 2 bleeding events. The event adrenal hemorrhage was considered treatment-emergent but the event of hemorrhagic stroke was not considered treatment-emergent.

Note: Subject 11355-600015092 was not considered treatment-emergent because the event started before study medication intake.

Other Bleeding Events

The following table summarizes the other bleeding events in the RECORD studies. There were more clinical relevant non-major bleeding events and any bleeding events with rivaroxaban than with enoxaparin in both patients undergoing hip and knee replacement surgeries.

Other Bleeding Events in RECORD 1-4

Bleeding Events	THR: RECORD 1-2		TKR: RECORD 3-4		Overall	
	Rivaroxaban N=3437	Enoxaparin N=3453	Rivaroxaban N=2746	Enoxaparin N=2747	Rivaroxaban N=6183	Enoxaparin N=6200
Any Bleeding	214(6.2%)	199(5.7%)	220 (8.0%)	202 (7.4%)	434 (7.0%)	401 (6.5%)
Clinically relevant non-major bleeding	105(3.1%)	87(2.5%)	72 (2.6%)	58 (2.1%)	177 (2.9%)	145 (2.3%)
Other non-major bleeding event	114(3.3%)	113(3.3%)	146(5.3%)	143(5.2%)	260 (4.2%)	256 (4.1%)

Non-major clinically relevant bleeding event categories are shown in table below. The most frequently reported non-major bleeding events for the both treatment groups were excessive wound hematomas and surgical site bleedings. More patients experienced macroscopic hematuria, rectal bleeding, nose bleeding, and vaginal bleeding in the rivaroxaban group as compared to enoxaparin group.

Components of Treatment-emergent Non-major Clinically Relevant Bleeding Events (as Assessed by Central Adjudication Committee) (Subjects Valid for Safety in pooled RECORD 1-4 studies)

Endpoint	Rivaroxaban (N = 6183)		Enoxaparin (N = 6200)	
Any event	177	(2.86%)	145	(2.34%)
Excessive wound hematoma	53	(0.86%)	58	(0.94%)
Surgical site bleeding	47	(0.76%)	49	(0.79%)
Macroscopic hematuria[a]	28	(0.45%)	8	(0.13%)
Rectal bleeding	20	(0.32%)	6	(0.10%)
Hematemesis	11	(0.18%)	14	(0.23%)
Nose bleeding (>5 minutes)	8	(0.13%)	4	(0.06%)
Vaginal bleeding	8	(0.13%)	2	(0.03%)
Gingival bleeding (>5 minutes)	2	(0.03%)	3	(0.05%)
Intra-articular with trauma	2	(0.03%)	3	(0.05%)
Unexpected hematoma (>25 cm^2)	2	(0.03%)	2	(0.03%)
Coughing blood	1	(0.02%)	2	(0.03%)
Rehospitalization or prolongation of hospitalization	1	(0.02%)	1	(0.02%)
Blood in semen	1	(0.02%)	0	(0.00%)
Multiple source bleeding	1	(0.02%)	0	(0.00%)

[a] Either spontaneous or lasting more than 24 hours if associated with an intervention.
Note: Only bleeding event categories that were observed in at least 1 subject are shown
Note: Results based on total duration pool.

Additional analysis for adjudicated bleeding events in different pools.

The sponsor performed additional analysis using combined adjudicated bleeding events and different pooling method for bleeding events.

The following table summarizes the pooled incidence of treatment-emergent adjudicated bleeding events from the 4 RECORD studies and presents data for the total duration pool, the Day 12 ± 2 day pool, and the active control pool. The "total duration pool" considered all events occurring during the administration of double-blind study medication, including events occurring during the placebo period of RECORD 2. The "Day 12 ± 2 pool" considered events occurring during the double-blind period until Day 12 ± 2. The "active control pool" considered events occurring during the active control period from each of the RECORD studies (events occurring during the placebo period of RECORD 2 were excluded).

The incidence of treatment-emergent adjudicated bleeding events was higher in the rivaroxaban group as compared to the enoxaparin group for the various bleeding categories in all three duration pool analyses.

The incidence of major bleeding combined with surgical-site bleeding events was also higher, with a total of 111 (1.8%) and 85 (1.4%) events in the rivaroxaban and enoxaparin groups respectively, with a study-stratified hazard ratio of 1.3 (95% CI: 1.0, 1.7, p=0.082). There were 197 (3.2%) and 158 (2.6%) treatment-emergent major or non-major clinically-relevant adjudicated bleeding events, with a study-stratified hazard ratio of 1.3 (95% CI: 1.0 to 1.5%, p=0.039). The incidence of any treatment-emergent bleeding event was higher in the rivaroxaban group than in the enoxaparin group (434 [7.0%] and 401 [6.5%], respectively) hazard ratio of

1.1, 95% CI: 0.9, 1.2, p=0.255. Similar results were seen based on the Day 12 ± 2 and active control pool analyses.

Incidence of Treatment-emergent Bleeding Events (as Assessed by Central Adjudication Committee) (Subjects Valid for Safety in pooled RECORD 1-4 studies)

Endpoint	Rivaroxaban (N = 6183)	Enoxaparin (N = 6200)	Absolute Risk difference (95% CI)	Hazard Ratio[c] (95% CI)	Hazard Ratio P Value
Major bleeding event (total duration)[a]	24 (0.39%)	13 (0.21%)	0.18% (-0.01%, 0.37%)	1.84 (0.94, 3.62)	0.076
Major bleeding event until Day 12 ± 2[a]	21 (0.34%)	13 (0.21%)	0.13% (-0.05%, 0.31%)	1.61 (0.81, 3.22)	0.175
Major bleeding event – active control phase	23 (0.37%)	13 (0.21%)	0.16% (-0.03%, 0.35%)	1.77 (0.90, 3.49)	0.101
Major bleeding combined with surgical site bleeding events (total duration)[b]	111 (1.80%)	85 (1.37%)	0.42% (-0.01%, 0.86%)	1.31 (0.99, 1.73)	0.063
Major bleeding combined with surgical site bleeding events until Day 12 ± 2[b]	108 (1.75%)	84 (1.35%)	0.39% (-0.04%, 0.83%)	1.29 (0.97, 1.71)	0.082
Major bleeding combined with surgical site bleeding events – active control phase	110 (1.78%)	84 (1.35%)	0.42% (-0.01%, 0.86%)	1.31 (0.99, 1.74)	0.061
Major or non-major clinically relevant bleeding event (total duration)	197 (3.19%)	158 (2.55%)	0.64% (0.05%, 1.23%)	1.25 (1.01, 1.54)	0.039
Major or non-major clinically relevant bleeding event until Day 12 ± 2	176 (2.85%)	152 (2.45%)	0.40% (-0.17%, 0.96%)	1.16 (0.93, 1.44)	0.186
Major or non-major clinically relevant bleeding event, active control phase	190 (3.07%)	156 (2.52%)	0.56% (-0.02%, 1.14%)	1.22 (0.99, 1.51)	0.068
Any bleeding event (total duration)	434 (7.02%)	401 (6.47%)	0.53% (-0.35%, 1.42%)	1.08 (0.94, 1.24)	0.255
Any bleeding event until Day 12 ± 2	409 (6.61%)	384 (6.19%)	0.40% (-0.46%, 1.26%)	1.06 (0.93, 1.22)	0.376
Any bleeding event – active control phase	424 (6.86%)	397 (6.40%)	0.44% (-0.44%, 1.31%)	1.07 (0.93, 1.22)	0.348

[a] The protocol pre-specified definition of major bleeding restricted events to those that were extrasurgical for clinically overt bleeding events leading to a decrease in hemoglobin or requiring a blood transfusion.

[b] This definition of major bleeding includes events occurring at the surgical site associated with a decrease in hemoglobin of at least 2 g/dL or for bleedings requiring transfusion of 2 or more units of whole blood or packed cells. Surgical-site bleeding events associated with a decrease in hemoglobin were based on a determination by the investigator. Surgical-site bleeding events requiring transfusion were based on an algorithmic assessment of blood transfusions given within 48 hours of the bleeding event. In addition, both types of surgical-site bleeding events must have been based on bleeding events confirmed by the adjudication committee and reported as overt surgical-site bleeding events by the investigator.

[c] This is a Cox-regression analysis with study treated as a covariate.

Note: Total duration refers to the total duration pool (see Section 1.2.4.2).

Key: CI = confidence interval

The incidence of adjudicated, treatment-emergent bleeding events for various bleeding categories in each of the RECORD studies individually based on the total duration pool is shown in the following table. For most of the categories, the incidence was higher on rivaroxaban compared to enoxaparin in all studies. It was noted that there was a higher incidence rate of other non-major (non-clinically relevant) bleeding and also any bleeding in the RECORD 4 study as compared to RECORD 1, 2, and 3 for both treatment groups.

Incidence of Treatment-emergent Bleeding by Study
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety in pooled RECORD 1-4 studies)

Endpoint / Study	Rivaroxaban)		Enoxaparin	
Major bleeding event				
RECORD 1	6/2209	(0.27%)	2/2224	(0.09%)
RECORD 2	1/1228	(0.08%)	1/1229	(0.08%)
RECORD 3	7/1220	(0.57%)	6/1239	(0.48%)
RECORD 4	10/1526	(0.66%)	4/1508	(0.27%)
All studies pooled	24/6183	(0.39%)	13/6200	(0.21%)
Non-major clinically relevant bleeding event				
RECORD 1	65/2209	(2.94%)	54/2224	(2.43%)
RECORD 2	40/1228	(3.26%)	33/1229	(2.69%)
RECORD 3	33/1220	(2.70%)	28/1239	(2.26%)
RECORD 4	39/1526	(2.56%)	30/1508	(1.99%)
All studies pooled	177/6183	(2.86%)	145/6200	(2.34%)
Other (non-clinically relevant) non-major bleeding event				
RECORD 1	71/2209	(3.21%)	77/2224	(3.46%)
RECORD 2	43/1228	(3.50%)	36/1229	(2.93%)
RECORD 3	22/1220	(1.80%)	31/1239	(2.50%)
RECORD 4	124/1526	(8.13%)	112/1508	(7.43%)
All studies pooled	260/6183	(4.21%)	256/6200	(4.13%)
Major bleeding combined with surgical site bleeding event				
RECORD 1	40/2209	(1.81%)	33/2224	(1.48%)
RECORD 2	23/1228	(1.87%)	19/1229	(1.55%)
RECORD 3	21/1220	(1.72%)	17/1239	(1.37%)
RECORD 4	27/1526	(1.77%)	16/1508	(1.06%)
All studies pooled	111/6183	(1.80%)	85/6200	(1.37%)
Major or non-major clinically relevant bleeding event				
RECORD 1	70/2209	(3.17%)	56/2224	(2.52%)
RECORD 2	41/1228	(3.34%)	34/1229	(2.77%)
RECORD 3	40/1220	(3.28%)	34/1239	(2.74%)
RECORD 4	46/1526	(3.01%)	34/1508	(2.25%)
All studies pooled	197/6183	(3.19%)	158/6200	(2.55%)
Any bleeding event				
RECORD 1	133/2209	(6.02%)	131/2224	(5.89%)
RECORD 2	81/1228	(6.60%)	68/1229	(5.53%)
RECORD 3	60/1220	(4.92%)	60/1239	(4.84%)
RECORD 4	160/1526	(10.48%)	142/1508	(9.42%)
All studies pooled	434/6183	(7.02%)	401/6200	(6.47%)

Note: Only bleeding event categories that were observed in at least 1 subject are shown
Note: Results based on total duration pool.

Consistent with what was observed in the 4 RECORD studies pooled, in the THR pool, the incidence of events in the various bleeding categories was higher on rivaroxaban as compared to enoxaparin. The incidence of major bleeding was 0.2% in the Rivaroxaban group as compared to 0.09% in the enoxaparin group in patients undergoing total hip replacement surgery. The incidence of non-major clinically relevant bleeding events was 3.05% in the rivaroxaban group as compared to 2.52% in the enoxaparin group.

Incidence of Treatment-emergent Bleeding by Study
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety in pooled RECORD 1 and 2 studies)

Endpoint Study	Rivaroxaban N=3437	Enoxaparin N=3453	Hazard Ratio* (95% CI)	Hazard Ratio p-value
Major bleeding event	7(0.20%)	3(0.09%)	2.34 (0.60,9.04)	p=0.219
Non-major clinically relevant bleeding event	105(3.05%)	87(2.52%)	Not done	Not done
Other (non-clinically relevant) non-major bleeding event	114(3.32%)	113(3.27%)	Not done	Not done
Major bleeding combined with surgical site bleeding event	63(1.83%)	52(1.51%)	1.21 (0.84,1.75)	p=0.302
Major or non-major clinically relevant bleeding event	111(3.23%)	90(2.61%)	1.23 (0.93,1.63)	p=0.141
Any bleeding event	214(6.23%)	199(5.76%)	1.08 (0.89,1.30)	p=0.459

* This is a Cox-regression analysis with study treated as a covariate.
N = numerator; D = denominator
Note: Only bleeding event categories that were observed in at least 1 subject are shown
Note: Results based on total duration pool.

In the TKR pool, the incidence of events in the various bleeding categories was higher on rivaroxaban as compared to enoxaparin (see table below). The incidence of major bleeding was 0.62% in the rivaroxaban group as compared to 0.36% in the enoxaparin group inpatients undergoing the total knee replacement surgery. The incidence of non-major clinically relevant bleeding event was 2.62% in the rivaroxaban group as compared to 2.11% in the enoxaparin group.

**Incidence of Treatment-emergent Bleeding by Study
(as Assessed by Central Adjudication Committee)
(Subjects Valid for Safety in pooled RECORD 3 and 4 studies)**

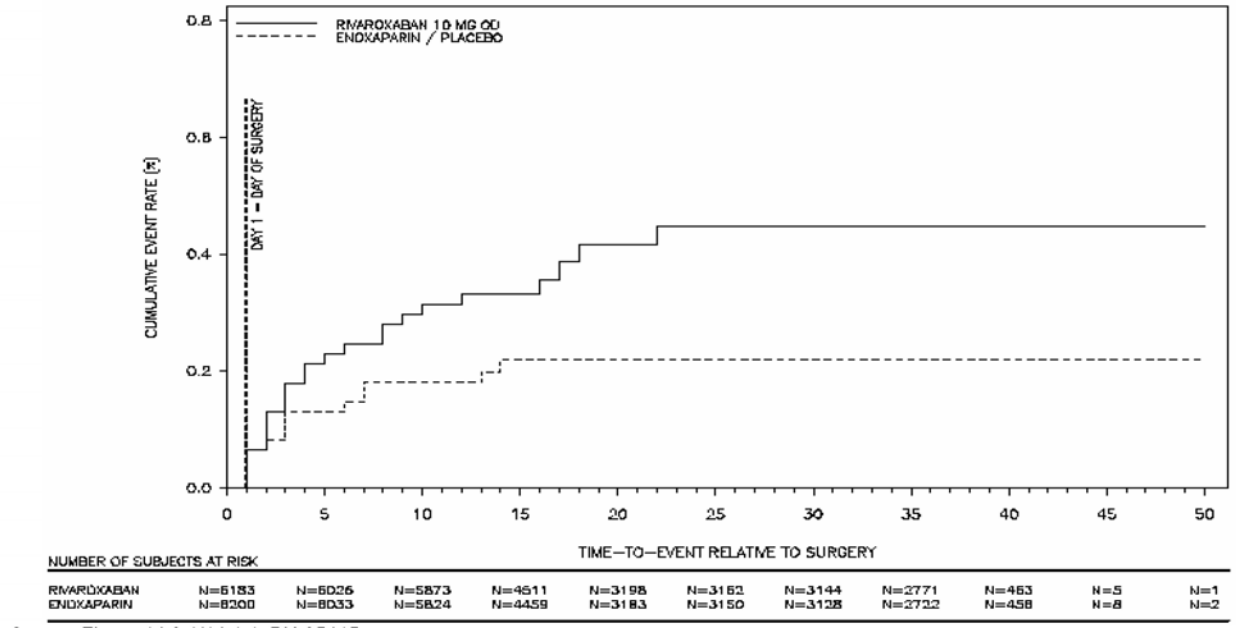
Endpoint Study	Rivaroxaban N=2746	Enoxaparin N=2747	Hazard Ratio* (95% CI)	Hazard Ratio p-value
Major bleeding event	17(0.62%)	10(0.36%)	1.70 (0.78,3.70)	p=0.185
Non-major clinically relevant bleeding event	72(2.62%)	58(2.11%)	Not done	Not done
Other (non-clinically relevant) non-major bleeding event	146(5.32%)	143(5.21%)	Not done	Not done
Major bleeding combined with surgical site bleeding event	48(1.75%)	33(1.20%)	1.46 (0.94,2.27)	p=0.096
Major or non-major clinically relevant bleeding event	86(3.13%)	68(2.48%)	1.27 (0.92,1.74)	p=0.145
Any bleeding event	220(8.01%)	202(7.35%)	1.09 (0.90,1.32)	p=0.380

* This is a Cox-regression analysis with study treated as a covariate.
N = numerator; D = denominator
Note: Only bleeding event categories that were observed in at least 1 subject are shown
Note: All bleeding events that occurred more than 2 days after the last intake of study medication are not included.
Note: Results based on total duration pool.

Timing of Bleeding Events

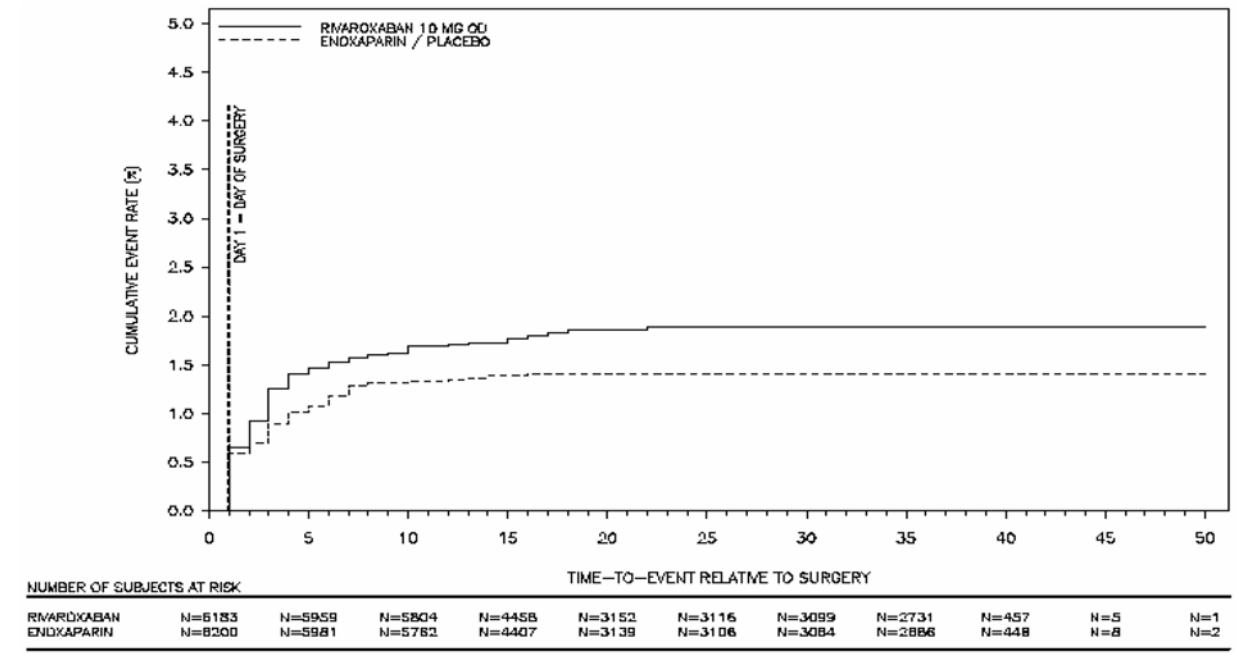
The following figure shows the Kaplan Meier plot of the time to any first major bleeding event. The two curves began to separate 2 days after surgery. The treatment-emergent major bleeding events occurred by Day 7 in 15 (63%) rivaroxaban subjects and 11 (85%) enoxaparin subjects.

Figure 1-1: Cumulative Rate (Kaplan Meier) of Treatment-emergent Major Bleeding Events (Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)



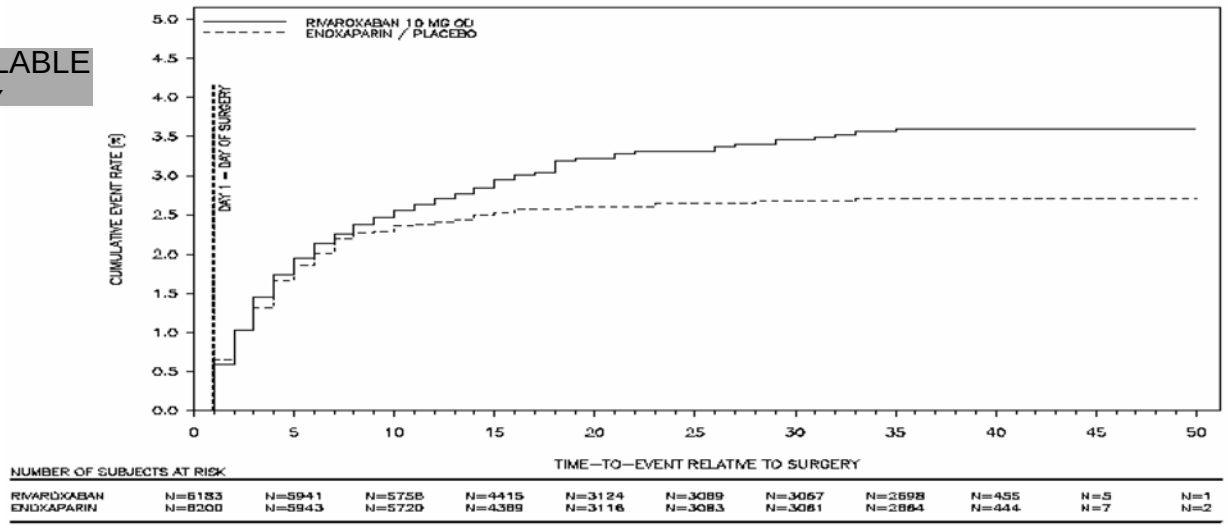
The following figure shows the time to event for major bleeding combined with surgical bleeding events. Most major bleeding events combined with surgical site bleeding events, occurred within a few days of surgery. The 2 curves begin to separate by Day 2 with separation maintained thereafter.

Figure 1-2: Cumulative Rate (Kaplan Meier) of Treatment-emergent Major Bleeding Events Including Surgical Site (Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)



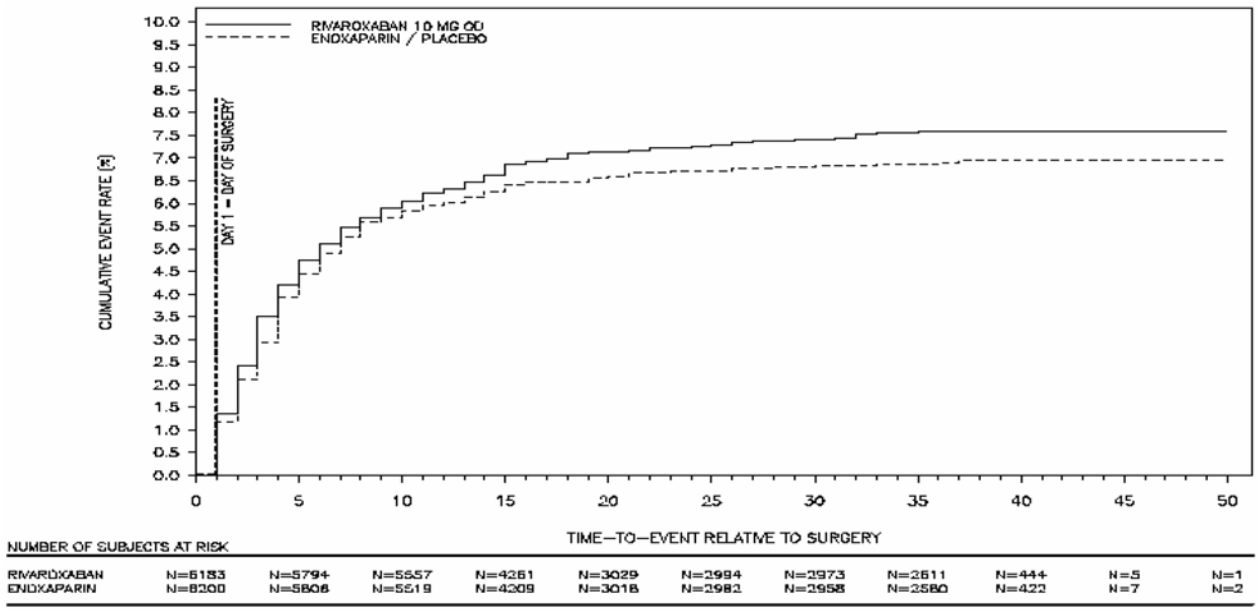
Major or non-major clinically relevant bleeding events occurred by Day 7 in 137 [69.5%] rivaroxaban subjects and 134 [84.8%] enoxaparin subjects, respectively (see figure below). The separation between the 2 curves occurred from Day 8 with separation becoming wider over the next 27 days and was maintained thereafter.

Figure 1-3: Cumulative Rate (Kaplan Meier) of Treatment-emergent Major or Non-major Clinically Relevant Bleeding Ever (Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)



The following figure shows the Kaplan Meier plot of the time to any first bleeding event. A majority of the bleeding events occurred by Day 7: 73.9% on rivaroxaban and 77.3% on enoxaparin.

Figure 1-4: Cumulative Rate (Kaplan Meier) of Event: Any Treatment-Emergent Bleeding Events (Population: Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)



The time to bleeding event results for each RECORD study were similar to the pooled RECORD 1-4 studies. Major bleeding events that began more than 2 days after last dose of study drug occurred in 4 (0.06%) subjects in both the rivaroxaban and enoxaparin groups. A total of 12 (0.19%) rivaroxaban subjects and 17 (0.27%) enoxaparin subjects had major or non-major clinically-relevant bleeding events during this period.

Surgical and Extrasurgical Site Bleeding

Slightly more than half of all reported bleeding events were surgical-site bleeding events. A total of 14 (0.2%) rivaroxaban and 7 (0.1%) enoxaparin subjects had treatment-emergent major surgical-site bleeding events (see table below). Of the 14 surgical-site bleeding events with rivaroxaban classified as major, 12 were bleeding events requiring reoperation, 1 was a fatal bleed in a subject who was randomized to rivaroxaban but never received active study medication, and 1 subject who was initially reported as a surgical-site bleed by the investigator, was subsequently adjudicated as an extrasurgical-site bleeding by the Adjudication Committee. Of the 7 enoxaparin major bleeding events, all were bleeding events that required re-operation. A majority (77 [69.4%] and 72 [68.6%]) of non-major, clinically relevant surgical-site bleeding events occurred by Day 4 in the rivaroxaban and enoxaparin treatment groups, respectively. The remainder of the events occurred after this time period.

Incidence of Treatment-emergent Surgical Site Bleeding Events
(Subjects Valid for Safety in pooled RECORD 1-4 studies)

Endpoint	Rivaroxaban (N=6183)		Enoxaparin (N=6200)	
Major bleeding event	14[a]	(0.23%)	7	(0.11%)
Any major or non-major clinically relevant bleeding event	111	(1.80%)	105	(1.69%)
Any bleeding event	247	(3.99%)	224	(3.61%)

[a] One subject who was initially reported with a surgical site bleed by the investigator, was later reported with an extrasurgical site bleeding by the Adjudication Committee.
Note: Results based on total duration pool.
Note: Subjects who experienced surgical site bleeding events and extrasurgical site bleeding events are counted separately in Tables 1-19 and 1-20.

The occurrence of major or non-major clinically relevant extrasurgical site bleeding events was relatively delayed compared with surgical site bleeding events. A total of 10 (0.2%) rivaroxaban and 6 (0.1%) enoxaparin subjects had treatment-emergent major surgical-site bleeding events. A total of 33 (36.2%) and 30 (54.5%) major or non-major, clinically relevant extrasurgical site bleeding events occurred by Day 4 in the rivaroxaban and enoxaparin arms, respectively (see Table below). The remainder of the 91 and 55 events in the rivaroxaban and enoxaparin arms, respectively, occurred after Day 4 with most occurring by Day 10.

Incidence of Treatment-emergent Extrasurgical Site Bleeding Events (Subjects Valid for Safety in pooled RECORD 1-4 studies)

Endpoint	Rivaroxaban (N=6183)		Enoxaparin (N=6200)	
Major bleeding event	10	(0.16%)	6	(0.10%)
Any major or non-major clinically relevant bleeding event	91	(1.47%)	55	(0.89%)
Any bleeding event	206	(3.33%)	191	(3.08%)

Note: Results based on total duration pool.

Bleeding Risk in Subgroups

The following figures show the hazard ratio of rivaroxaban relative to enoxaparin and its 95% CI for major or non-major clinically relevant bleeding events and any bleeding event using pooled RECORD 1-4 data in the subgroup analyses. The results in the majority of subgroups were consistent with the results seen in the overall population showing more bleeding events with Rivaroxaban treatment than with enoxaparin.

In certain subgroups, such as Asian subjects, subjects with body weight ≤50 kg or >110 kg, BMI<18.5 or ≥40, the risk of major or non-major clinically relevant bleeding events appeared to be higher with rivaroxaban as compared to other groups.

The results of the subgroup analysis of any bleeding event are generally similar to the subgroup results observed with major or non-major clinically relevant bleeding events. In most subgroups, the results were consistent with results from the overall RECORD population. Asian subjects appear to have a higher risk of any bleeding event with rivaroxaban than other subjects.

Figure 1-5: Major and Non-major Clinically Relevant Bleeding Events and Corresponding Hazard Ratios (95% CI) by Subgroups

(Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)

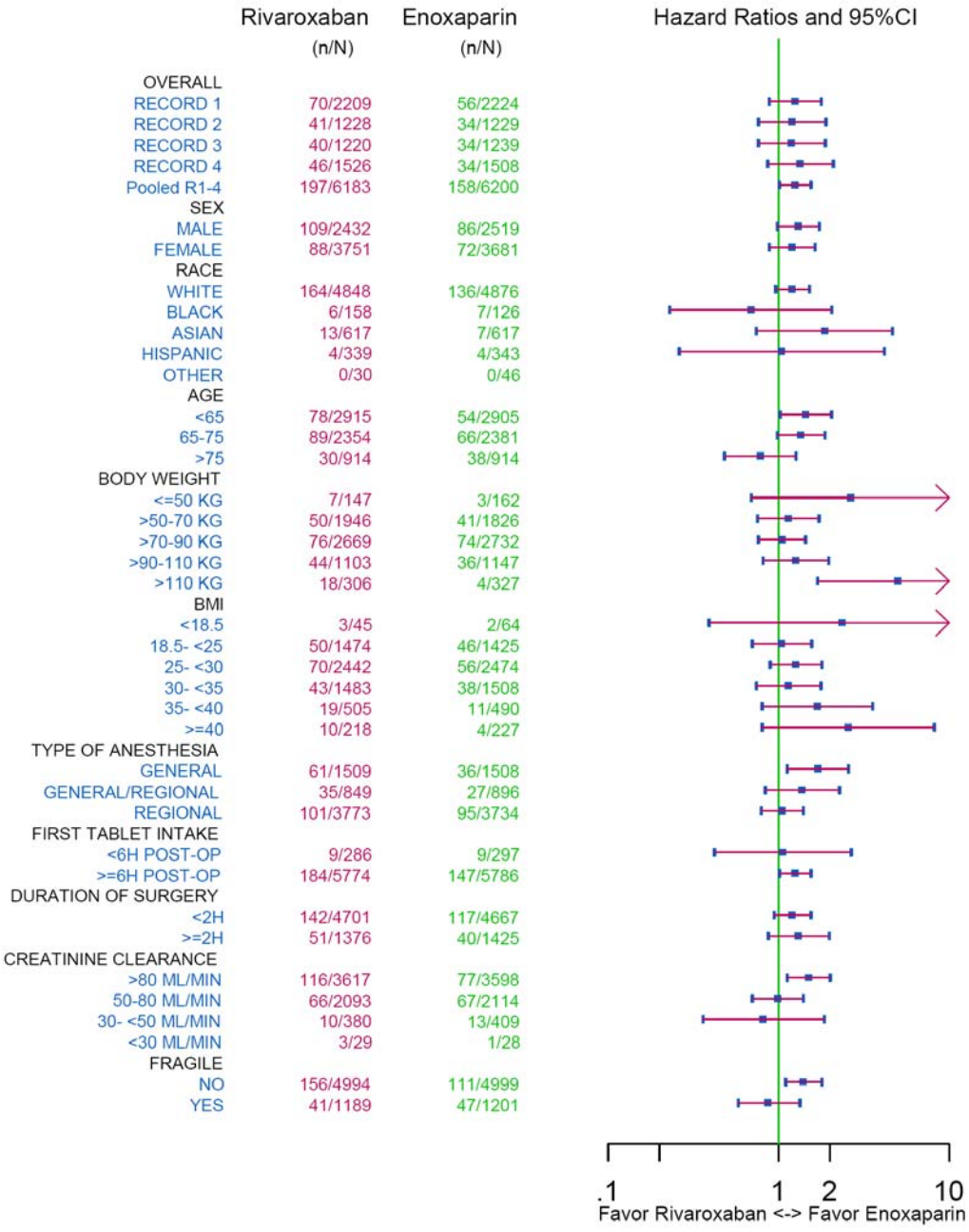
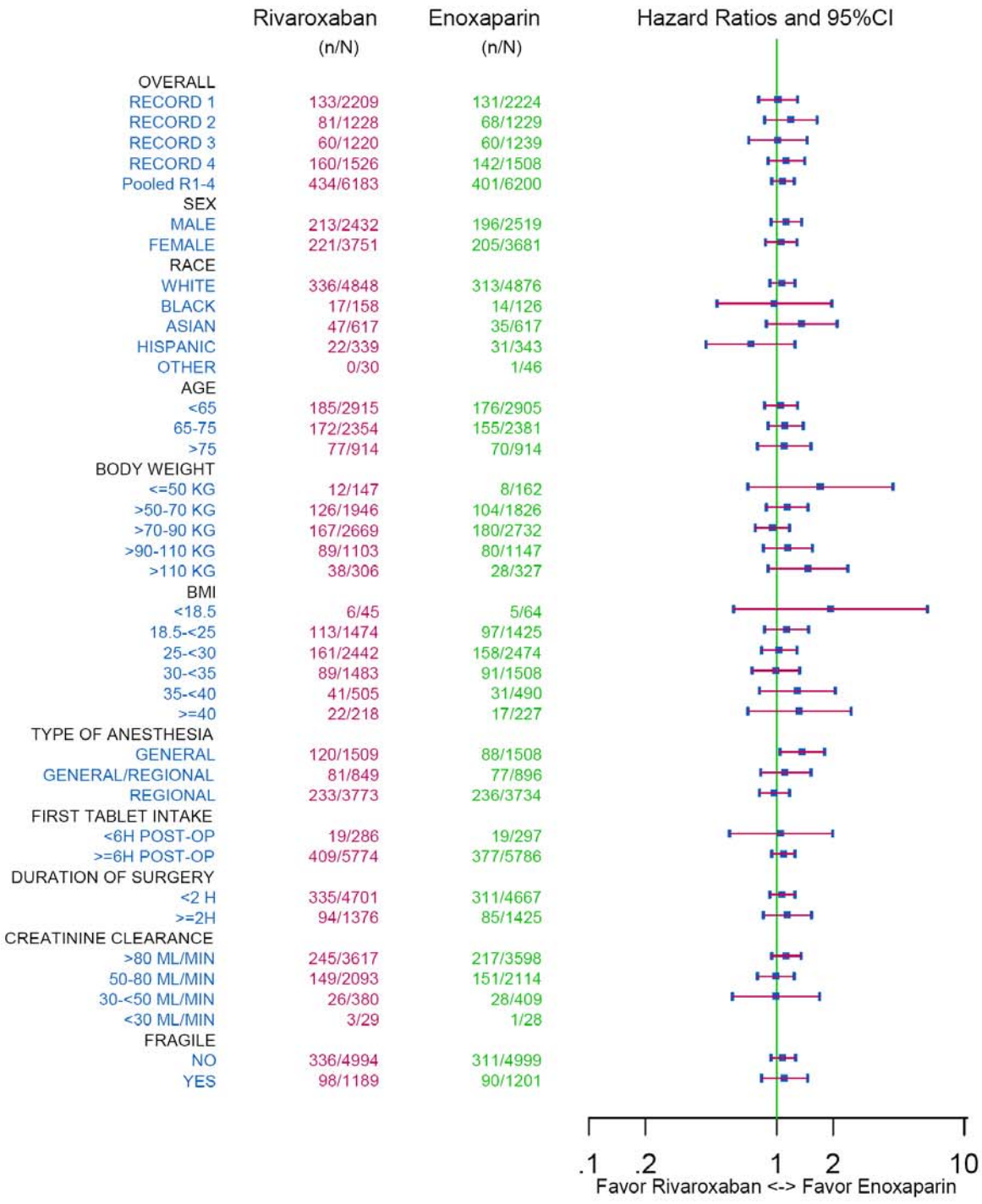


Figure 1-6: Any Bleeding Events and Corresponding Hazard Ratios (95% CI) by Subgroups

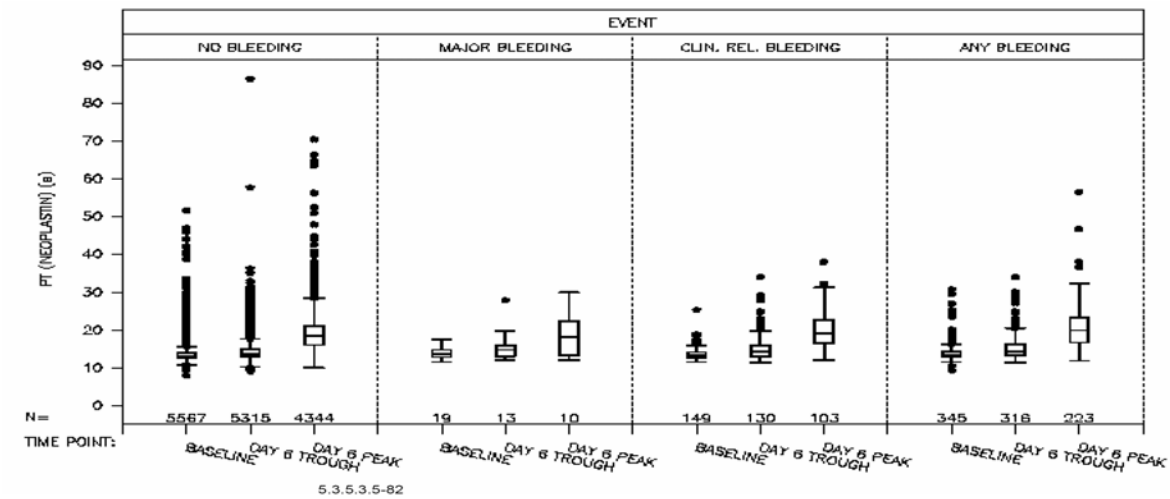
(Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)



Bleeding Risk and Correlation to Prothrombin Time Prolongation

A total of 4,373 subjects in the rivaroxaban arm had baseline and Day 6 peak and trough prothrombin time (PT) measurements. The baseline, Day 6 trough, and Day 6 peak mean ± standard deviation PT values were 13.5 ± 2.0, 14.3 ± 2.7, and 19.0 ± 4.5 seconds, respectively. About 90% of subjects had Day 6 peak PT between 13.3 and 26.4 seconds, 5% had Day 6 peak PT ≤13.3 seconds, and 5% had Day 6 peak PT ≥26.4 seconds. The following Figure shows the distribution of PT values observed at baseline, Day 6 trough, and Day 6 peak in subjects without any bleeding events, subjects with major bleeding events, subjects with clinically relevant non-major bleeding events, and subjects with any bleeding events. Bleeding events occurring until Day 12 ± 2 are considered in the Figure. It appears that there is no significant difference in PT values in subjects experiencing bleeding events compared with subjects who were not experiencing bleeding events.

Figure 1-7: Distribution of the Coagulation Parameter Prothrombin Time (in seconds) in Subjects with or without Bleeding Events (Day 12 ± 2 pool) (Subjects Valid for Safety Analysis in pooled RECORD 1-4 studies)



The Box-Whisker Plots in Figures 14.4/6, PH-35408 show the following: The upper and lower boundaries of the box indicate the upper quartile and lower quartile, respectively. The line inside the box indicates the median. The vertical lines below and above the box (whiskers), extend (at most) a distance of 1.5 times the length of the box. The whiskers end at the smallest or largest observed value within the 1.5 inter-quartile range. Values below or above the whiskers are denoted as "outliers" and plotted as stars.

Investigator-Assessed Bleeding Events

A total of 428 (6.9%) and 412 (6.7%) rivaroxaban and enoxaparin subjects, respectively, had investigator-assessed, treatment-emergent bleeding events. A total of 64 (1.0%) and 47 (0.8%) rivaroxaban and enoxaparin subjects, respectively had investigator-assessed serious treatment-emergent bleeding events. The most common bleeding events were hematoma, which occurred in 10 (0.2%) rivaroxaban and 10 (0.2%) enoxaparin subjects; operative hemorrhage, which occurred in 11 (0.2%) and 7 (0.1%) rivaroxaban and enoxaparin subjects, respectively; and wound hemorrhage, occurring in 3 (0.1%) and 6 (0.1%) rivaroxaban and enoxaparin subjects, respectively. A total of 50 (0.8%) and 36 (0.6 %) rivaroxaban and enoxaparin subjects, respectively, experienced bleeding adverse events resulting in permanent study drug discontinuation. The most common adverse bleeding events leading to discontinuation were

hematuria (5 [0.1%] and 0 [0%] of rivaroxaban and enoxaparin, respectively), operative hemorrhage (5 [0.1%] and 9 [0.2%] of rivaroxaban and enoxaparin subjects, respectively), epistaxis (3 [<0.1%] of rivaroxaban and enoxaparin subjects), and hematoma (3 [<0.1%] of rivaroxaban and enoxaparin subjects).

Intraoperative Blood Loss and Blood Transfusion

The intraoperative blood loss in the THR studies (RECORD 1 and 2) was 479.7 ± 337.2 mL and 491.7 ± 357.6 mL on rivaroxaban and enoxaparin, respectively. The intraoperative blood loss in the TKR studies (RECORD 3 and 4) was 203.7 ± 240.4 mL and 196.1 ± 205.1 mL on rivaroxaban and enoxaparin, respectively. Similarly, the incidence of blood transfusion was higher in the hip studies compared with the knee studies. In the RECORD 1 and 2 hip studies, a total of 1695 (49.3%) and 1763 (51.1%) subjects, respectively received any blood transfusion. In the RECORD 3 and 4 knee studies, a total of 1247 (45.5%) and 1172 (42.7%) subjects, respectively, received any blood transfusion.

7.3.4.2 Cardiovascular Events

According to the operation manual, the Cardiovascular Events Adjudication Committee (AC/CV) adjudicated all investigator-identified cases of death (cardiovascular or non-cardiovascular), myocardial infarction or stroke. Originally, in RECORD 1 and 2, the AC/CV adjudicated only CV deaths identified by the sponsor medical monitor. Twenty-one CV events in 19 subjects were observed in the rivaroxaban group and 14 CV events in 14 subjects were observed in the enoxaparin group. Two subjects in the rivaroxaban group, both in RECORD 1, experienced 2 events; the first subject (180214015) had an MI on treatment (Day 8) and a CV death off treatment (Day 34), and the second subject (360044014) had an MI off treatment (Day 44) and an ischemic stroke off treatment (Day 69).

After the databases for RECORD 1 and 2 were unblinded, all deaths were sent to the AC/CV for the retrospective adjudication and these included 14 deaths (2 in the rivaroxaban group and 12 in the enoxaparin group) that had not originally been sent to the AC/CV for adjudication. In addition, one identified MI was also sent for the retrospective adjudication. The MI (RECORD 2 subject 260077025) was adjudicated as “no MI” by the AC/CV. The 14 deaths consisted of 5 subjects in RECORD 1 (1 in the rivaroxaban group and 4 in enoxaparin group) and 9 subjects in RECORD 2 (1 in the rivaroxaban group and 8 in the enoxaparin group). The AC/CV adjudicated these 14 cases in a fully blinded fashion, and did not re-adjudicate or reassess any of the originally adjudicated events. Of these 14 additional deaths that underwent adjudication by the AC/CV, 5 deaths were classified as “CV-death”, and 1 as “unexplained death”, all of these events occurred in the enoxaparin group, and no other CV events were identified in the rivaroxaban group. One subject with an “unexplained death” (RECORD 2 subject 370087001) had already had a prior adjudicated event of ischemic stroke entered into the database. After retrospective adjudication for RECORD 1 and 2 studies, a total of 20 CV events in 19 subjects

were identified in the enoxaparin group and the data for the rivaroxaban group were unchanged as a total of 21 CV events in 19 subjects.

In RECORD 3 and 4, all deaths were sent for adjudication by the AC/CV.

The following table presents retrospectively adjudicated cardiovascular events that occurred in the safety population during study drug treatment and during the 30-day post-study drug follow-up in the 4 RECORD studies. There was one subject in the rivaroxaban group with an adjudicated event of ischemic stroke (occurring 8 days after last dose of study drug) who was not included in the clinical database because the adjudicated results were not available prior to database unblinding. This subject is included in the table below. The total number of cardiovascular events (centrally adjudicated myocardial infarction, stroke and death) during treatment and follow-up was 31 events (0.50%) in the rivaroxaban group and 39 events (0.63%) in the enoxaparin group.

A total of 12 (0.19%) adjudicated ischemic events were observed in the rivaroxaban group as compared to 7 (0.11%) ischemic stroke events in the enoxaparin group.

There was one rivaroxaban subject in whom an adverse event preferred term of "lacunar infarction" was reported; however, this potential event was not sent for adjudication because the investigator indicated that it was a pre-existing condition. This event occurred while the subject was on study drug.

In addition, 3 subjects in the enoxaparin group with a suspected myocardial infarction were considered not assessable by the AC/CV and are not included.

In the enoxaparin group, more than half (21 [54%]) of the events occurred through Day 6. In the rivaroxaban group, 12 (40%) of the total number of events occurred through Day 6.

Incidence of Cardiovascular Events (Retrospective Central Adjudication)
(Subject Valid for Safety in pooled RECORD 1-4 studies)

Preferred Term	**Rivaroxaban (N=6183)**	**Enoxaparin (N=6200)**
Any cardiovascular events	31 (0.50%)	39 (0.63%)
Myocardial infarction	13 (0.21%)	18 (0.29%)
Ischemic stroke	12 (0.19)	7 (0.11%)
Cardiovascular death	7 (0.11%)	12 (0.19%)
Unexplained death	1 (0.02%)	4 (0.06%)

The following table shows the cardiovascular events during on and off treatment period in RECORD studies. Cardiovascular events on active treatment are those that occur after first intake of active study medication and no later than 1 day after last intake of active study

medication. Cardiovascular events off active treatment are those that occur later than 1 day after last intake of active study medication. The 1-day window for differentiating on-active treatment versus off-active treatment events was pre-specified.

The incidence of on-active treatment cardiovascular events was lower in subjects in the rivaroxaban group (13 [0.2%]) compared with enoxaparin (25 [0.4%]). The ischemic stroke event rates were similar between the two treatment groups during the treatment period. Cardiovascular events occurring off active treatment were slightly more in subjects in the rivaroxaban group (17, 0.3%) than in the enoxaparin group (14, 0.2%).

Among the 17 subjects who experienced cardiovascular events in the rivaroxaban group and 14 in the enoxaparin group during the off-treatment period, 11 (66%) events (4 MI, 3 stroke and 4 CV deaths) in the rivaroxaban group and 2 (14%) events (1 CV death and 1 unexplained death) in the enoxaparin group occurred within 10 days after the last dose of treatment; 7 (41%) events (2 MI, 2 stroke, and 3 CV deaths) in the rivaroxaban group and 1 (7%) events (CV death) in the enoxaparin group occurred within 5 days after the last dose of treatment.

There were more ischemic stroke events in subjects in the rivaroxaban group (6, 0.10%) than in the enoxaparin group (1, 0.02%) during the off treatment period. The 6 stroke events occurred in 4, 5, 8, 13, 34, and 39 days after the last dose of treatment in 6 subjects. One stroke event in the enoxaparin group occurred 26 days after the last dose of treatment.

**Incidence of Cardiovascular Events (Retrospective Adjudication)
During On and Off Treatment Period in RECORD 1-4
(Subjects Valid for Safety with Active Study Drug in pooled RECORD 1-4 studies)**

	On Treatment		Off Treatment	
Preferred Term	**Rivaroxaban (N=6183)**	**Enoxaparin (N=6200)**	**Rivaroxaban (N=6183)**	**Enoxaparin (N=6200)**
Any cardiovascular events	13 (0.21)	25 (0.40)	17 (0.28)	14 (0.23)
Myocardial infarction	7 (0.11)	14 (0.23)	5 (0.08)	4 (0.06)
Ischemic stroke	5 (0.08)	6 (0.10)	6 (0.10)	1 (0.02)
Cardiovascular death	1 (0.02)	5 (0.08)	6 (0.10)	6 (0.10)
Unexplained death	0	0	1 (0.02)	4 (0.06)

7.3.4.3 Wound Complications

The incidence of any wound complication event was higher on rivaroxaban compared with enoxaparin. The incidence of infectious surgical wound complications was balanced between the 2 treatment groups. The incidence of non-infectious wound complications was higher on rivaroxaban compared with enoxaparin. The preferred term 'wound secretion' was the most commonly reported noninfectious wound complication and was responsible for most of the increase. The majority of reported wound secretion adverse events were mild in severity. The incidence of any wound complication serious adverse event was comparable on rivaroxaban 46 (0.7%) and enoxaparin 47 (0.8%). The event of "any wound complication" adverse events resulting in permanent discontinuation of study drug occurred in 3 (0.1%) and 10 (0.2%) of subjects on rivaroxaban and enoxaparin, respectively.

Incidence of Treatment-emergent Wound Complications
(Subjects Valid for Safety in pooled RECORD 1-4 studies)

Endpoint Studies	Rivaroxaban (N =6183)		Enoxaparin (N =6200)	
Surgical Wound Complications				
Any event	332	(5.37%)	280	(4.52%)
Surgical wound complications, infectious				
Any event	78	(1.26%)	82	(1.32%)
Postoperative wound infection	27	(0.44%)	28	(0.45%)
Wound infection	38	(0.61%)	35	(0.56%)
Surgical wound complications, non-infectious				
Any event	269	(4.35%)	206	(3.32%)
Wound complication	39	(0.63%)	31	(0.50%)
Wound secretion	146	(2.36%)	106	(1.71%)

Key: MedDRA = Medical Dictionary Regulatory Activities
Note: Only treatment-emergent adverse event that occurred up to 2 days after the last dose of study medication are included.
Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the event after the start of treatment
Note: The table presents MedDRA terms of the primary path

7.3.4.4 Hepatic Events

7.3.4.4.1 RECORD Studies

Abnormal Liver-related Laboratory Values

The liver-related laboratory parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, alkaline phosphatase (ALK PHOS), and gamma-

glutamyltransferase [GGT]) were assessed on Days 0, 1, 6, 13, 36, and 65 (follow-up) for RECORD 1 and 2 and on Days 0, 1, 6, 13, and 42 (follow-up) for RECORD 3 and 4. In all 4 studies, Day 1 laboratory assessments were performed after surgery but prior to the administration of the first oral dose of study drug (rivaroxaban or matching dummy placebo tablet) but after the first injection dose of the study drug (enoxaparin or matching dummy placebo injection) in RECORD 1-3.

The following table shows the incidence of liver-related laboratory abnormalities post-baseline in pooled RECORD studies. The elevation of ALT>3xULN was observed in 152 (2.5%) subjects in the rivaroxaban group as compared to 227 (3.7%) subjects in the enoxaparin group. For ALT abnormality, there were fewer patients with ALT >3xULN, >5xULN, and >8xULN in the Rivaroxaban group as compared to the enoxaparin group. However, for ALT >10xULN and >20xULN, there was 1 more patient in the rivaroxaban group than in the enoxaparin group for each category. There were slightly more patients with total bilirubin (TB) >1.5xULN in the rivaroxaban group as compared to the enoxaparin group.

There were 9 (0.15%) patients who had ALT >3xULN concurrent with TB >2xULN in the rivaroxaban group as compared to 7 (0.11%) patients in the enoxaparin group. Concurrent refers to laboratory analyses drawn from the same sample. These subjects will be discussed later in this review.

There were 10 subjects in the rivaroxaban group and 9 subjects in the enoxaparin group with elevations in ALT levels to >10x ULN. In nearly all cases, the liver enzyme elevations returned or were returning to <1x ULN while study drug was continued or after study drug discontinuation. One subject in RECORD 4 (11355-600095028) received rivaroxaban for 10 days and subsequently had an ALT level >10x ULN approximately 6 weeks (45 days) after the last dose of study drug. Additional follow-up on this subject after the RECORD 4 study results were unblinded revealed that ALT levels had normalized 2 weeks later. In addition, 1 subject in RECORD 2 (11357-120087009) received enoxaparin for 9 days and subsequently had an ALT level >10x ULN one day later (Day 10). This subject had incomplete laboratory follow-up.

There were 8 (0.13%) patients who had AST levels >3x ULN concurrent with TB >2x ULN in each treatment groups.

With respect to elevations of ALT levels >3x ULN concurrent with total bilirubin levels >2x ULN with the ratio of conjugated to total bilirubin ≥0.5, there were 4 and 5 such cases observed in the rivaroxaban and enoxaparin arms, respectively.

There were fewer subjects with AST >3xULN and high categories, ALK PHOS> 3xULN and GGT>3xULN in rivaroxaban group than in the enoxaparin group.

Pooled Incidence Rates of Liver-related Post-baseline Laboratory Abnormalities – After Day 0 Baseline
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

Laboratory Variable Limit	Rivaroxaban (N=6183)		Enoxaparin (N=6200)	
ALT >3x ULN concurrent with total bilirubin >2x ULN				
	9/6131	(0.15%)	7/6131	(0.11%)
ALT >3x ULN concurrent with total bilirubin >2x ULN and conjugated bilirubin ≥0.5 total bilirubin				
	4/6131	(0.07%)	5/6130	(0.08%)
ALT				
>3x ULN	152/6131	(2.48%)	227/6131	(3.70%)
>5x ULN	56/6131	(0.91%)	78/6131	(1.27%)
>8x ULN	18/6131	(0.29%)	20/6131	(0.33%)
>10x ULN	10/6131	(0.16%)	9/6131	(0.15%)
>20x ULN	2/6131	(0.03%)	1/6131	(0.02%)
AST >3x ULN concurrent with total bilirubin >2x ULN				
	8/6131	(0.13%)	8/6131	(0.13%)
AST >3x ULN concurrent with total bilirubin >2x ULN and conjugated bilirubin ≥0.5 total bilirubin				
	5/6131	(0.08%)	6/6130	(0.10%)
AST				
>3x ULN	160/6131	(2.61%)	209/6131	(3.41%)
>5x ULN	61/6131	(0.99%)	84/6131	(1.37%)
>8x ULN	28/6131	(0.46%)	29/6131	(0.47%)
>10x ULN	19/6131	(0.31%)	20/6131	(0.33%)
>20x ULN	4/6131	(0.07%)	4/6131	(0.07%)
Total bilirubin				
>1.5x ULN	169/6133	(2.76%)	158/6131	(2.58%)
>2x ULN	48/6133	(0.78%)	48/6131	(0.78%)
>3x ULN	10/6133	(0.16%)	11/6131	(0.18%)
>5x ULN	2/6133	(0.03%)	4/6131	(0.07%)
>8x ULN	1/6133	(0.02%)	1/6131	(0.02%)
Alkaline phosphatase				
>3x ULN	20/6133	(0.33%)	21/6132	(0.34%)
>5x ULN	0/6133	(0.00%)	1/6132	(0.02%)
>8x ULN	0/6133	(0.00%)	0/6132	(0.00%)
>10x ULN	0/6133	(0.00%)	0/6132	(0.00%)
>20x ULN	0/6133	(0.00%)	0/6132	(0.00%)
GGT				
>3x ULN	401/6133	(6.54%)	553/6132	(9.02%)
>5x ULN	139/6133	(2.27%)	211/6132	(3.44%)
>8x ULN	38/6133	(0.62%)	75/6132	(1.22%)
>10x ULN	15/6133	(0.24%)	33/6132	(0.54%)
>20x ULN	0/6133	(0.00%)	4/6132	(0.07%)

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyltransferase; ULN = upper limit of normal
Note: The scheduled Day 0 visit is used as baseline.
Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the abnormality after Day 0
at risk = # of subjects with values after Day 0
Note: All measurements after the start of double-blind study medication are included regardless of onset relative to the last dose.
Note: The subjects reported in higher threshold categories are also included in lower threshold categories.

An additional analysis was performed for liver-related laboratory abnormalities by race. In the RECORD studies, there were about 80% Caucasians, 10% Asians and 10% of subjects with other races. The following table shows the liver-related abnormalities in two treatment groups in Asian and Caucasian. It was noted that there were significantly higher incidence of ALT>3xULN and TB>2xULN in the rivaroxaban group (4, 0.65%) than in the enoxaparin group (1, 0.16%) in Asians but it was not seen in Caucasians. The four Asian in the rivaroxaban group were from China, Indonesia, India and Seri Lanka, respectively. The one Asian in enoxaparin group was from India. There were also higher rate of ALT>10 xULN and >20xULN with rivaroxaban than with enoxaparin in Asian. The difference between the races was not seen for other abnormalities.

Incidence Rates of Liver-Related Abnormalities in RECORD 1-4 in Asian and Caucasian

	Asian		**Caucasian**	
LFTs and others	**Rivaroxaban**	**Enoxaparin**	**Rivaroxaban**	**Enoxaparin**
ALT >3x ULN and TB>2x ULN	4 / 614 (0.65%)	1/611 (0.16%)	4 / 4811 (0.08%)	5 / 4817 (0.10%)
ALT> 3x ULN	20 / 614 (3.26%)	34/611 (5.56%)	118 / 4811(2.45%)	166 / 4817 (3.45%)
>5x ULN	6 / 614 (0.98%)	13/611 (2.13%)	44 / 4811 (0.91%)	55 / 4817 (1.14%)
> 8x ULN	5 / 614 (0.81%)	5/611 (0.82%)	12 / 4811 (0.25%)	12 / 4817 (0.25%)
> 10x ULN	4 / 614 (0.65%)	2/611 (0.33%)	6 / 4811 (0.12%)	6 / 4817 (0.12%)
> 20x ULN	2 / 614 (0.33%)	1/611 (0.16%)	0 / 4811 (0.00%)	0 / 4817 (0.00%)
AST >3x ULN and TB>2x ULN	4 / 614 (0.65%)	1/611 (0.16%)	3 / 4811 (0.06%)	7 / 4817 (0.15%)
AST >3x ULN	17 / 614 (2.77%)	26/611 (4.26%)	128 / 4811 (2.66%)	166 / 4817 (3.45%)
>5x ULN	5 / 614 (0.81%)	8/611 (1.13%)	49 / 4811 (1.02%)	55 / 4817 (1.14%)
>8x ULN	4 / 614 (0.65%)	4/611 (0.65%)	21 / 4811 (0.44%)	12 / 4817 (0.25%)
>10x ULN	4 / 614 (0.65%)	3/611 (0.49%)	13 / 4811 (0.27%)	6 / 4817 (0.12%)
>20x ULN	1 / 614 (0.16%)	1/611 (0.16%)	3 / 4811 (0.06%)	0 / 4817 (0.00%)
TB >1.5x ULN	50 / 614 (8.14%)	50/611 (8.18%)	110 / 4813 (2.29%)	97 / 4817 (2.01%)
>2x ULN	14 / 614 (2.28%)	12/611 (1.96%)	32 / 4813 (0.66%)	31 / 4817 (0.64%)
ALP >3x ULN	3 / 614 (0.49%)	2/611 (0.33%)	14 / 4813 (0.29%)	17 / 4818 (0.35%)
GGT >3x ULN	25 / 614 (4.07%)	30/611 (4.91%)	313 / 4813 (6.50%)	429 / 4818 (8.90%)

ALT Elevations Over Time

There were mean increases in ALT levels in both the THR and TKR studies occurring on Days 6 and 13 in both treatment groups. There was more increase from baseline on Days 6 and 13 in the enoxaparin group compared with rivaroxaban in both the THR and TKR studies (see Tables below).

Mean (SD) Changes from Day 0 Baseline in ALT Levels in THR trials (Subjects Valid for Safety in RECORD 1 and 2)

	Rivaroxaban Mean (SD) U/L	Enoxaparin Mean (SD) U/L
Day 0 (baseline)	22.1 (13.0)	22.4 (14.2)
Change from baseline (Day 1)	-0.4 (22.6)	-1.1 (15.4)
Change from baseline (Day 6 ± 2)	12.0 (30.3)	18.8 (65.2)
Change from baseline (Day 13 ± 2)	7.2 (24.2)	14.5 (33.4)
Change from baseline (Day 36 ± 4)	-2.7 (26.8)	1.0 (18.9)
Change from baseline (Day 65 + 5)	-1.6 (12.5)	-1.7 (15.0)

Key: ALT = alanine aminotransferase; SD = standard deviation
Note: The scheduled Day 0 visit is used as baseline; when earlier visits are present, the last value up to and including Day 0 is used as baseline.
Note: If more than 1 measurement is available for a subject at the same visit, the mean value is used for analysis.
Note: Only subjects having a non-missing baseline assessment and at least 1 non-missing postbaseline assessment are included.

Mean (SD) Changes from Day 0 Baseline in ALT Levels in TKR Trials (Subjects Valid for Safety in RECORD 3 and 4)

	Rivaroxaban Mean (SD) U/L	Enoxaparin Mean (SD) U/L
Day 0 (baseline)	22.2 (13.2)	21.8 (12.0)
Change from baseline (Day 1)	0.0 (20.0)	1.0 (23.5)
Change from baseline (Day 6 ± 2)	8.1 (31.1)	12.6 (29.4)
Change from baseline (Day 13 ± 2)	4.7 (21.2)	13.1 (31.3)
Change from baseline (Day 42 + 5)	-2.4 (26.8)	-2.5 (12.2)

Key: ALT = alanine aminotransferase; SD = standard deviation
Note: The scheduled Day 0 visit is used as baseline; when earlier visits are present, the last value up to and including Day 0 is used as baseline.
Note: If more than 1 measurement is available for a subject at the same visit, the mean value is used for analysis.
Note: Only subjects having a non-missing baseline assessment and at least 1 non-missing postbaseline assessment are included.

The time to first occurrence (after Day 0) of ALT levels >3x ULN is presented in the following tables for THR and TKR trials. In the THR studies, there were more subjects with first ALT levels >3x ULN events on Day 1 but fewer after Day 1 in the rivaroxaban group than in the enoxaparin group. In the TKR studies, there were more subjects with first ALT levels >3x ULN events on interim Days 1-6 and ≥Day 42 but fewer on other days on rivaroxaban compared with enoxaparin.

Time to First Occurrence of ALT> 3x ULN After Day 0 in THR Trials (Subjects Valid for Safety in THR - RECORD 1 and 2)

	Rivaroxaban		Enoxaparin	
Time Point	Number of Events/Number of Subjects w/ Labs	Event Rate	Number of Events/Number of Subjects w/ Labs	Event Rate
Day 1	18/3307	(0.54%)	11/3314	(0.33%)
Interim Days 1 - 6	1/28	(3.57%)	1/26	(3.85%)
Day 6 (± 2 days)	40/2928	(1.37%)	67/2922	(2.29%)
Interim Days 6 – 13	1/15	(6.67%)	2/28	(7.14%)
Day 13 (± 2 days)	20/3135	(0.64%)	34/3100	(1.10%)
Interim Days 13 - 36	0/25	(0.00%)	0/32	(0.00%)
Day 36 (± 4 days)	3/3043	(0.10%)	10/2964	(0.34%)
Interim Days 36 - 65	0/16	(0.00%)	0/10	(0.00%)
≥Day 65 (± 5 days)	4/2897	(0.14%)	7/2848	(0.25%)
Total time period	87		132	

Key: ALT = alanine aminotransferase; Labs = laboratory results; ULN = upper limit of normal
Note: Measurements taken more than 2 days after the end of treatment are included.
Note: Subjects with abnormality at Day 0 or Day 0 value only are not included.
Note: An "interim" assessment is a laboratory assessment at a non-protocol scheduled timepoint.

Time to First Occurrence of ALT> 3x ULN After Day 0 (Subjects Valid for Safety in TKR - RECORD 3 and 4)

	Rivaroxaban		Enoxaparin	
Time Point	Number of Events/Number of Subjects w/ Labs	Event Rate	Number of Events/Number of Subjects w/ Labs	Event Rate
Day 1	20/2642	(0.76%)	30/2644	(1.13%)
Interim Days 1 - 6	2/17	(11.76%)	0/8	(0.00%)
Day 6 (± 2 days)	27/2563	(1.05%)	32/2546	(1.26%)
Interim Days 6 – 13	0/22	(0.00%)	1/19	(5.26%)
Day 13 (± 2 days)	10/2486	(0.40%)	27/2471	(1.09%)
Interim Days 13 – 42	0/15	(0.00%)	0/24	(0.00%)
≥Day 42 (± 5 days)	4/2372	(0.17%)	2/2332	(0.09%)
Total time period	63		92	

Key: ALT = alanine aminotransferase; Labs = laboratory results; ULN = upper limit of normal
Note: Measurements taken more than 2 days after the end of treatment are included.
Note: Subjects with abnormality at Day 0 or Day 0 value only are excluded.
Note: An "interim" assessment is a laboratory assessment at a non-protocol scheduled timepoint.

The prevalence of subjects with ALT levels >3x ULN over time for the pooled RECORD studies is shown in Table below. A total of 40 rivaroxaban subjects [0.7%] and 43 enoxaparin subjects [0.7%] showed increased ALT levels on Day 1 before administration of rivaroxaban, due to the effects of surgery. The majority of subjects who had increased ALT levels experienced them in the period after surgery until Day 13. The prevalence of ALT levels >3x ULN after Day 13 was 0.3% and 0.5% in subjects receiving rivaroxaban and enoxaparin, respectively.

Prevalence of ALT >3x ULN by Time Windows in RECORD Studies (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

Visit/Time Window	Rivaroxaban		Enoxaparin	
Day 0	5/6103	(0.08%)	7/6109	(0.11%)
Day 1	40/5954	(0.67%)	43/5965	(0.72%)
After Day 1	119/6032	(1.97%)	188/6009	(3.13%)
Day 6 (± 2)	72/5529	(1.30%)	103/5513	(1.87%)
Day 13 (± 2)	39/5726	(0.68%)	71/5712	(1.24%)
Until Day 13 (± 2)	108/5992	(1.80%)	169/5971	(2.83%)
After Day 13 (± 2)	19/5648	(0.34%)	30/5614	(0.53%)

Key: ALT = alanine aminotransferase
Note: Day 0 visit scheduled prior to surgery
Note: Day 1 visit scheduled after surgery and prior to first tablet intake (active or dummy).
Note: In case of multiple measurements per visit/time window, the highest value is used.
Note: Measurements taken more than 2 days after the end of treatment are included.
Note: Time windows of "Until" and "After" include measurements from interim visits

The following Figures show the time course of ALT changes in individual subjects in each RECORD study who met the criteria for ALT levels >5x ULN at any time during the study on rivaroxaban and enoxaparin, respectively.

In the Record 1 study (see Figures below), the majority of peak elevations occur between Day 0 and Day 15, with a slightly shift to right in the rivaroxaban subjects as compared to enoxaparin subjects, followed by a decline back to baseline or <1x ULN either while study drug is continued or after study drug has been discontinued. There were 6 rivaroxaban subjects and 10 enoxaparin subjects who had a last measured ALT level >3x ULN.

Figure 1-1: Individual Plot of Subjects Administered Rivaroxaban with ALT >5x ULN at Any Time During the Study (Subjects Valid for the Safety Analysis in RECORD 1)

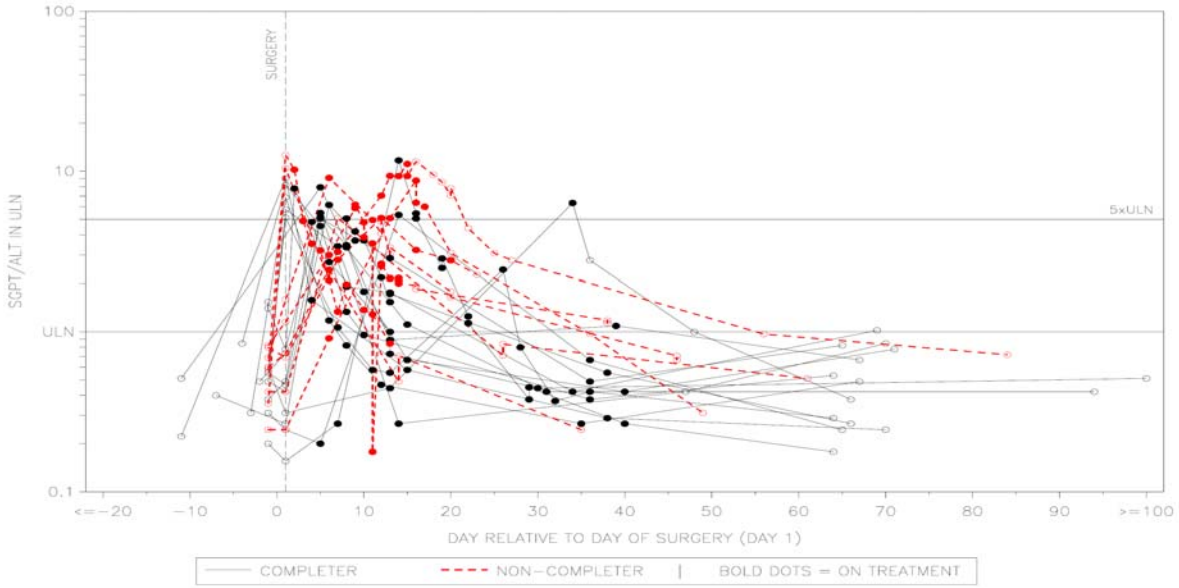
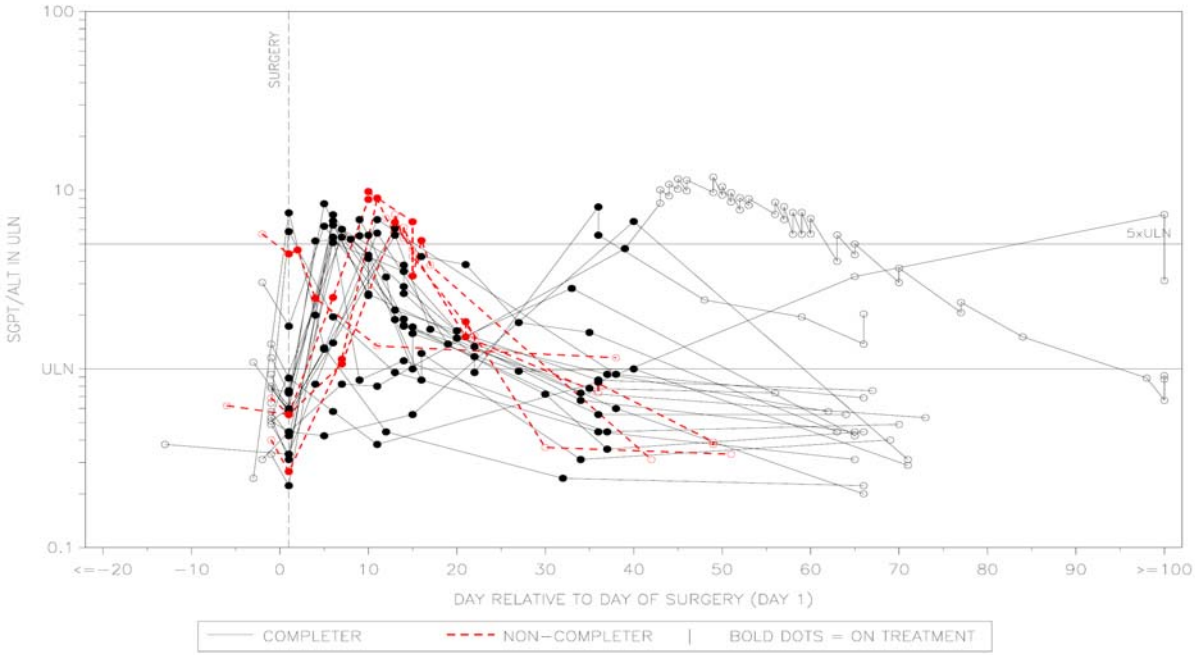
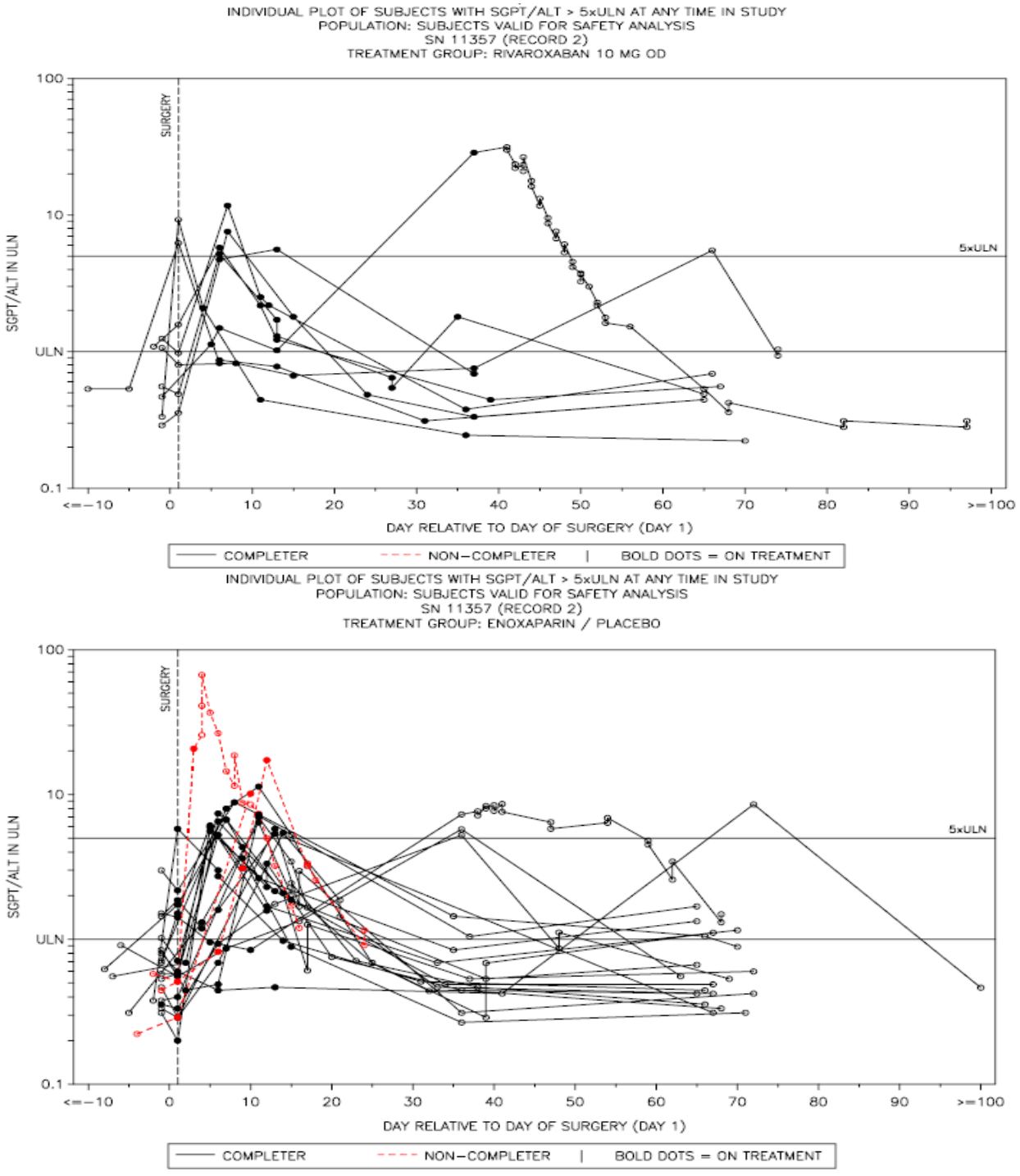


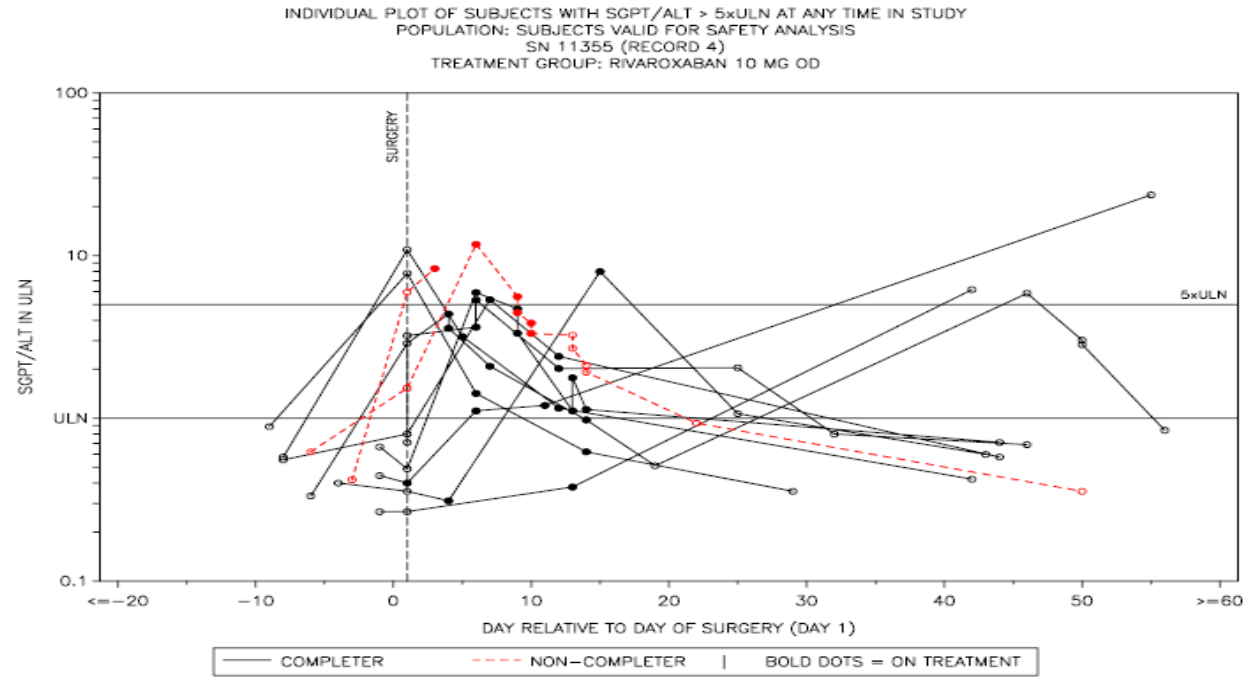
Figure 1-2: Individual Plot of Subjects Administered Enoxaparin with ALT >5x ULN at Any Time During the Study (Subjects Valid for the Safety Analysis in RECORD 1)

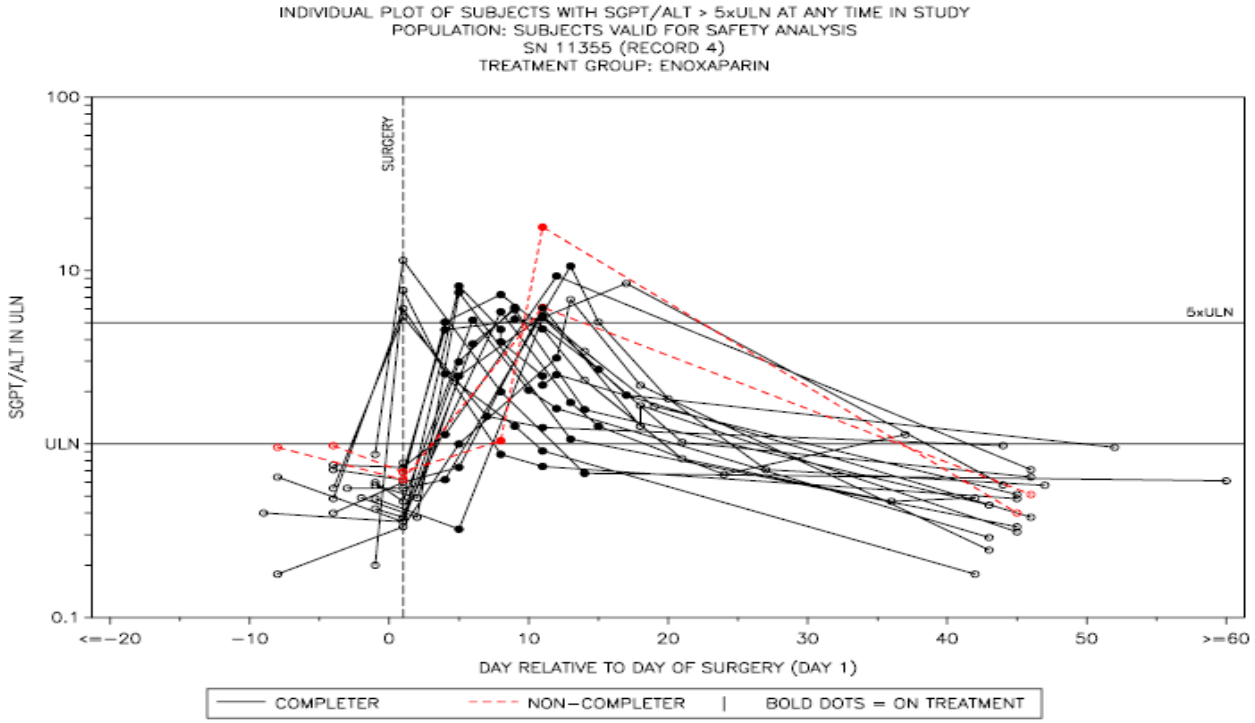


In RECORD 2 study (see Figure below), most subjects in both groups recovered quickly and few had late elevation of ALT and were back to normal in both groups.

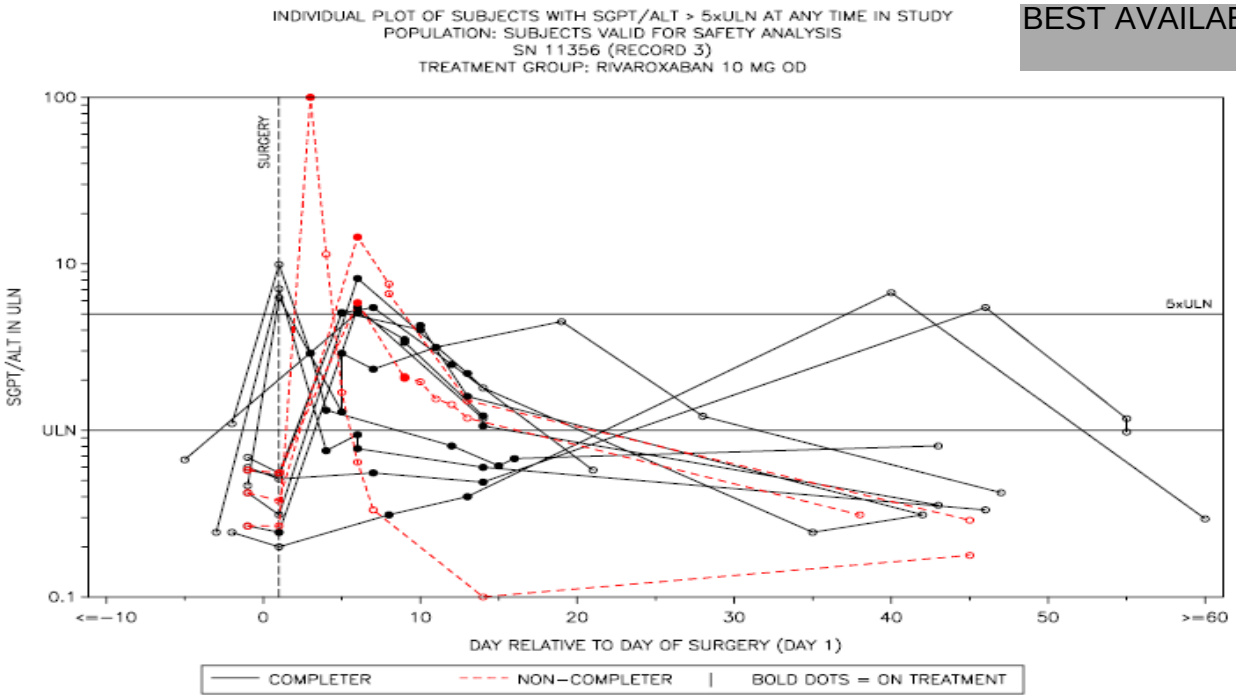


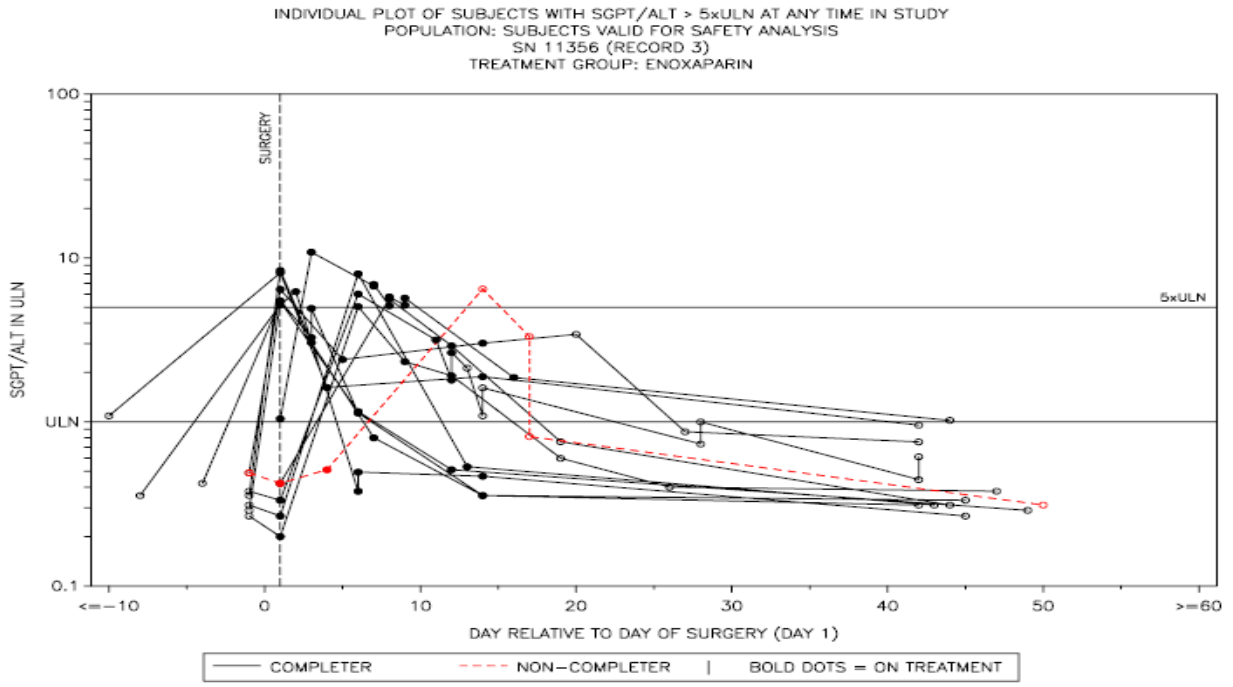
In RECORD 3 study (see figures below), 3 subjects in the rivaroxaban group had a late elevation of ALT >5 x ULN about 40-50 days after surgery, approximately 1 month after the last dose of treatment. One subject had normalized ALT and 2 had no further value available.





In RECORD 4 study (see Figure below), a late elevation of ALT >5 xULN was also noted in 2 subjects in the rivaroxaban group at 40-45 days after surgery, approximately 1 month after the last dose of treatment. Both subjects had normalized ALT about 2 weeks later.





Subjects with elevated liver enzymes at baseline were not excluded from enrollment in the RECORD studies. Subjects that entered the RECORD studies with an ALT level >1.5x ULN at

baseline (Day 0) did not show a worsening of ALT levels post baseline (while on study drug). Similar findings were seen in subjects with a baseline total bilirubin level >1.5x ULN.

ALT >3x ULN With a Concurrent Total Bilirubin >2x ULN

There were a total of 16 cases of ALT levels >3x ULN concurrent with a total bilirubin level >2x ULN in the RECORD studies. There were 9 subjects in the rivaroxaban group as compared to 7 in the enoxaparin group who met this criterion.

The following table lists the subjects with ALT levels >3x ULN concurrent with a total bilirubin level >2x ULN in the Rivaroxaban group in the RECORD studies along with the outcomes and Liver Advisory Panel (LAP) assessment for the subjects. Among those 16 subjects, 12 also had an elevated AST>3 xULN. Two rivaroxaban subjects experienced these elevations on the day of surgery (Day 1) before administration of rivaroxaban. The remaining 7 subjects had these elevations after Day 1.

Rivaroxaban: ALT >3x ULN Concurrent With TB>2x ULN Cases in RECORD 1-4 Studies

Age/ Sex/ Race/ ID	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment on role of study drug
83/M Unknown 11354-16009-4016 France	35	1	ALT 231 TB 3.3	Resolved on study drug. Subject with elevations in ALT/AST/TB on Day 1 (ALT>5xULN, AST>8xULN, and TB>2xULN after surgery but prior to 1st dose of active Rivaroxaban). ALT/AST/TB resolved while study drug continued. There was a re-elevation in ALT/AST (ALT>2 xULN and AST>2xULN) on Day 26 that normalized on Day 36.	Excluded
49/F White 11354-18003-4018 Poland	14	9	ALT 294 TB 2.5	Resolved after study drug discontinued. Subject with elevations in ALT/AST/TB on Day 6 and peaked on Day 9 (ALT>5xULN, AST>2xULN, and TB>2xULN). ALT/AST were resolving after study drug was stopped due to thrombocytopenia. ALT/AST were close to normal and TB>1.5xULN on Day 38. No further LFT values were available.	Possible related
32/M Asian 11357-54001-7029 China	33	11	ALT 166 TB 2.7	ALT increased again at follow-up. Subject with elevations of ALT/AST on Day 6 and peaked on Day 11 (ALT>3xULN and AST>2xULN). Total bilirubin was increased on Day 1 (TB>5xULN) which resolved while study drug continued. ALT/AST resolved by Day 27 while study drug continued. ALT increased >1.5xULN again on Day 67 and no further LFT values were available.	Possible related

52/M Asian 11357-55003-7007 Indonesia	36	37	ALT 1497 TB10.2	Hepatitis C was suspected. Subject with mild elevations of ALT/AST on Day 5-6 which was resolved on Day 13. Marked elevations of ALT/AST/TB on Day 37 (ALT>10xULN, AST>10xULN, and TB>3xULN) which gradually resolved over the next few weeks. Subject had nausea and darker urine 1 week before Day 36 visit, and was hospitalized on Day 42 with hepatomegaly and jaundice. The subject was treated by the remedial therapy including Vitamin B complex, pulverized curcuma roots (herb), and lecithin. ALT/AST/TB all normalized on Day 65. Investigator considered that these events were possible study drug related. The sponsor considered that these events were not study drug related and considered to be hepatitis C infection by serology and PCR tests.	Possible related by 1 member and unrelated by 2 members
60/F White 11356-22001-6007 Italy	12	7	ALT 246 TB 2.7	Resolved after study drug discontinued. Subject with elevations in ALT/AST/TB on Day 5 and peaked on Day 7 (ALT>5xULN, AST>3xULN and TB>2xULN). AST resolved by Day 12 and ALT/TB resolved by Day 21 after study drug was stopped.	Possible related
55/F White 11356-26010-6008 Canada	14	1	ALT 319 TB 3.0	Resolved on study drug. Subject with elevations in ALT/AST/TB on Day 1 (ALT>5xULN, AST>8xULN and TB>2xULN after surgery but before 1st dose of active rivaroxaban). These resolved in 2 days while study drug continued.	Unrelated
79/M White 11356-28018-6004 Belgium	9	6	ALT 263 TB 3.0	Resolved after study drug discontinued. Subject with elevations in ALT/AST/TB on Day 6 (ALT>5xULN, AST>3xULN, and TB>2xULN). Study drug was discontinued permanently due to this event. ALT/AST/TB all resolved on Day 38.	Possible/ Probable related
72/M Asian 11355-60009-5028 India	10	55	ALT 1062 TB 3.3	Insufficient follow-up. Mild elevation of ALT/AST on Day 6 and ALT on Day 11. Marked elevation of ALT/AST/TB on Day 55 (ALT>10xULN, AST>10xULN and TB>4xULN 45 days after last dose of study drug). No further LFT values were available. According to the sponsor that follow-up of lab values was obtained after the results of RECORD 4 were unblinded showed that there was resolution of ALT on Day 72.	Possible related
57/M Asian 11355-	9	6	ALT 528 TB 2.6	Resolved after study drug discontinued. Elevated ALT/AST on Day 1 that peaked on Day 6	Possible related

90002-5011 Sri Lanka				(ALT>10xULN, AST>10xULN and TB>3ULN). TB was elevated on Day 6. Study drug was discontinued permanently due to this event. ALT/AST/TB all resolved on Day 22.	

The following table shows the subjects with ALT levels >3x ULN concurrent with a total bilirubin level >2x ULN in the Enoxaparin group in RECORD studies.

Enoxaparin: ALT >3x ULN Concurrent With TB>2x ULN Cases in RECORD 1-4 Studies

Age/ sex	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment
74/M White 11354-180194037 Poland	15	14	ALT 190 /TB 3.5	Resolved after study drug discontinued. Elevated ALT/AST/TB on Day 14 (ALT>3xULN, AST>8xULN, and TB>2xULN). Study drug was discontinued permanently. Elevation resolved by Day 21.	Possible/ Probable related
85/M White 11357-120087009 United Kingdom	9	10	ALT 457 TB 3.8	Reported cholelithiasis and cholecystitis. Incomplete lab follow-up. ALT/AST/TB elevations on Day 10 (ALT>10xULN, AST>10xULN, and TB>3xULN). Study drug was discontinued permanently. Reported incomplete documentation of lab abnormality resolution. Increased liver enzyme elevations were attributed to cholecystitis.	Unrelated
64/F Other 11357-480057034 Colombia	12	7	ALT 146 TB 3.0	Resolved after study drug discontinued. ALT/AST elevated on Day 7 (ALT>3xULN, AST>1.5xULN and TB>2xULN). Study drug discontinued permanently. ALT/AST resolved on Day 24. TB elevated on Day 1 (TB>3xULN) and resolved by Day 13.	Possible related
40/F Asian 11355-600067001 India	2	3	ALT 3015 TB 6.6	Hypotension and acute renal failure were reported. Reported SAEs of hypotension and acute renal failure starting on Day 2 and study drug discontinued permanently. ALT/AST/TB first elevated on Day 3 (ALT 830, AST 1960, TB 3) with a peak on Day 4 (ALT 3015, AST 4500, TB 6.6) followed by gradual resolution over the next 2 weeks. Last follow-up labs on Day 16 where TB normalized and ALT/AST were nearly resolved.	Unlikely related

56/M White 11355-140015020 United States	12	12	ALT 418 TB 8.6	Reported obstruction of the common bile duct. ALT/AST/TB elevation first noted on Day 4 and peaked on Day 12 (ALT>8xULN, AST>5xULN, and TB>8xULN). Cholelithiasis was reported as an SAE on Day 15. These liver enzymes were resolved by Day 46.	Unlikely related
74/M White 11355-140205027 United States	10	11	ALT 801/TB 5.7	Resolved after study drug discontinued. ALT/AST/TB elevation peaked on Day 11 (ALT>10x ULN, AST>10x ULN, and TB>3xULN). Study drug discontinued permanently. ALT/AST/TB were normalized on Day 45.	Possible related
65/M White 11355-140205040 United States	2	2	ALT 191/TB 3.4	Absence of improvement after study drug discontinued. ALT/AST/TB elevation on Day 2 (ALT 3xULN, AST>2xULN, and TB>2xULN). Study drug discontinued permanently. ALT was mild elevation on Day 5 and 8 and normal on Day 10 and 12 and mild elevation on Day 16 and 19. AST normalized on Day 5. TB was elevated before surgery and remained elevated on Day 19. No further TB values were available.	Unlikely related

A Liver Advisory Panel (LAP) was established prior to the initiation of the RECORD studies to evaluate hepatic disorder adverse events of interest. This panel was managed by the Sponsor's Pharmacovigilance Department and provided the Sponsor with expert subspecialty opinion regarding the etiology of hepatic disorder adverse events. The panel consisted of independent external experts within 2 subteams (2 clinicians on the Clinical Subteam and 2 pathologists on the Pathology Subteam) with strong backgrounds in hepatology. Additional external consultants could be requested at any time. Each clinician on the Clinical Subteam was to independently and blindly review single cases based on all available medical records and provide a written assessment. In select cases where a liver biopsy or autopsy was performed, if tissue specimens were available, they were to be sent to the Pathology Subteam. The Liver Advisory Panel assessed liver-related adverse events in the Phase 3 RECORD studies in a blinded manner. Cases with the following criteria were to be assessed by the panel:

- Clinical symptoms of liver disease plus elevated liver-related laboratory tests
- Elevated liver-related laboratory tests reported as serious adverse events
- Liver disease with a fatal outcome
- ALT levels >3x ULN concurrent with total bilirubin >2x ULN
- Discontinuation of study medication due to elevation of liver-related laboratory tests

The Liver Advisory Panel operating procedures were amended to allow for an assessment by a single expert on the Clinical subteam. In most cases, only serious events were reviewed by the Liver Advisory Panel, although non-serious hepatic disorder adverse event cases could be sent as deemed necessary by the Sponsor's Pharmacovigilance Department; the more severe cases were to be assessed by at least 2 experts. Causality classification was to be assigned as definite, probably, possible, unlikely, excluded, or non assessable, however, some reviewers attributed events that were "excluded" as "unrelated."

As shown in Table below, most of the assessments were done by 2 clinicians under Clinical subteam. One case in the table (11355-60095028) was assessed as possible by LAP (Horsmans) after the NDA submission. Of the 16 cases in the table, one clinician (Horsmans) reviewed all cases. Of the 9 rivaroxaban cases, his assessment was that the role of rivaroxaban was excluded in 3 cases and possible in 6 cases. Of the 7 enoxaparin cases reviewed, his assessment was that the role of enoxaparin was excluded/unlikely in 4 cases, possible/probable in 3 cases. Six of the 16 cases were also reviewed by the second clinician (Maddrey) on the Clinical Subteam. There was agreement by the 2 members in 5 cases. In one case (Subject 11357-550037007), there was a disagreement between the 2 members. Additional clinician was involved. The following is the case with the disagreement involved.

This is a 52-year-old male without significant medical history and history of blood transfusion at past who was enrolled in RECORD 2 trial and received rivaroxaban for 35 days. The subject had marked elevation of liver enzymes on Day 37 on scheduled check-up, reported nausea and dark urine since Day 30. He was hospitalized on Day 42 for hepatomegaly, jaundice, nausea and vomiting, and was treated with vitamin B complex and herb medicine. The subject's condition improved on Day 56, discharged on Day 61, and liver enzyme normalized on Day 65. Hepatitis serology test showed non-reactive HCV-Ab at baseline and on Days 6, 13 and 37 but reactive on Days 47, 53 and 72. HCV-RNA PCR showed negative on Day 13, positive on Days 37, 47, 53, and negative again on Day 72. Blood sample from Day 86 showed quantitative and qualitative HCV-RNA-PCR (local lab) showed no virus. The subject refused any further blood drawing reporting that he felt very well. Retention samples at baseline also showed reactive IgG anti-HAV, HBsAg negative, positive HBs Ab, negative anti-HBc IgM and IgG. Blood sample on Day 72 also showed IgG anti-Toxoplasmosis, anti-Coxsackie (B2, B3, B4, B6). Investigator considered the event as study drug related. Hepatitis C was not listed in the case report form. The patient narrative and laboratory value are detailed in the narrative section following the table.

One LAP member (Maddrey) on the clinical subteam concluded that it is possible that the abnormalities seen were related to the study drug although hepatitis C must be considered as an alternative. There was a rather typical deceleration following drug removal and the peak laboratory values were noted in close proximity to the introduction of the drug. The patient did have elevated serum bilirubins in association with considerable elevations in aminotransferases suggesting the case enters the zone of concern. However there are certainly issues as to whether the patient had underlying chronic hepatitis C or developed a case of acute hepatitis C around the time of the event.

Another LAP member in the clinical subteam attributed these events to acute hepatitis C infection and the role of rivaroxaban was excluded.
An additional clinician considered these events to be unrelated to rivaroxaban treatment.

Liver Advisory Panel Assessments
(Cases of ALT >3x ULN Concurrent With Total Bilirubin >2x ULN)

Study Subject Number	Study Drug	Horsmans	Maddrey	Larrey	Pageaux
RECORD 1					
11354-160094016[a]	RIVA	5.3.5.3.6-14 excluded			
11354-180034018	RIVA	5.3.5.3.6-15 possible			
11354-180194037	ENOX	5.3.5.3.6-24 probable	5.3.5.3.6-25 possible/probable		
RECORD 2					
11357-120087009	ENOX	5.3.5.3.6-51 excluded	unrelated[b] 5.3.5.3.6-53		5.3.5.3.6-55 not related[b]
11357-480057034	ENOX	5.3.5.3.6-63 Possible			
11357-540017029	RIVA	5.3.5.3.6-67 possible			
11357-550037007	RIVA	5.3.5.3.6-80 excluded	5.3.5.3.6-86 possible	5.3.5.3.6-82 unrelated[b]	
11357-600067001	ENOX	5.3.5.3.6-95 unlikely			
RECORD 3					
11356-220016007	RIVA	5.3.5.3.6-104 possible	possible 5.3.5.3.6-105		
11356-260106008	RIVA	5.3.5.3.6-106 excluded	5.3.5.3.6-107 unrelated[b]		
11356-280186004	RIVA	5.3.5.3.6-112 possible	5.3.5.3.6-113 possible/probable		
RECORD 4					
11355-140015020	ENOX	5.3.5.3.6-144 unlikely			
11355-140205027	ENOX	5.3.5.3.6-151 possible			
11355-140205040	ENOX	5.3.5.3.6-154 unlikely			
11355-600095028[c]	RIVA				
11355-900025011	RIVA	5.3.5.3.6-161 possible			

[a] Narrative for this subject is related to a bleeding event since liver related lab abnormalities were not reported as a serious adverse event

[b] "Unrelated" or "not related" was the assessment provided by the Liver Advisory Panel expert; however, these terms are not included in the Causality Classification in the Liver Advisory Panel Manual of Operations.

[c] Not assessed by the Liver Advisory Panel

Key: ENOX = enoxaparin; RIVA = rivaroxaban

The following are patients' brief narratives and LFT graphs over time for subjects with ALT levels >3x ULN concurrent with a total bilirubin level >2x ULN. The graphs marked the day of first dose and day of last dose of active study medication (ASM). The x-axis of the figure shows

the time in days and the y-axis represents liver laboratory values as a ratio of the actual value to the upper limit of normal.

Rivaroxaban Group

11354-16009-4016

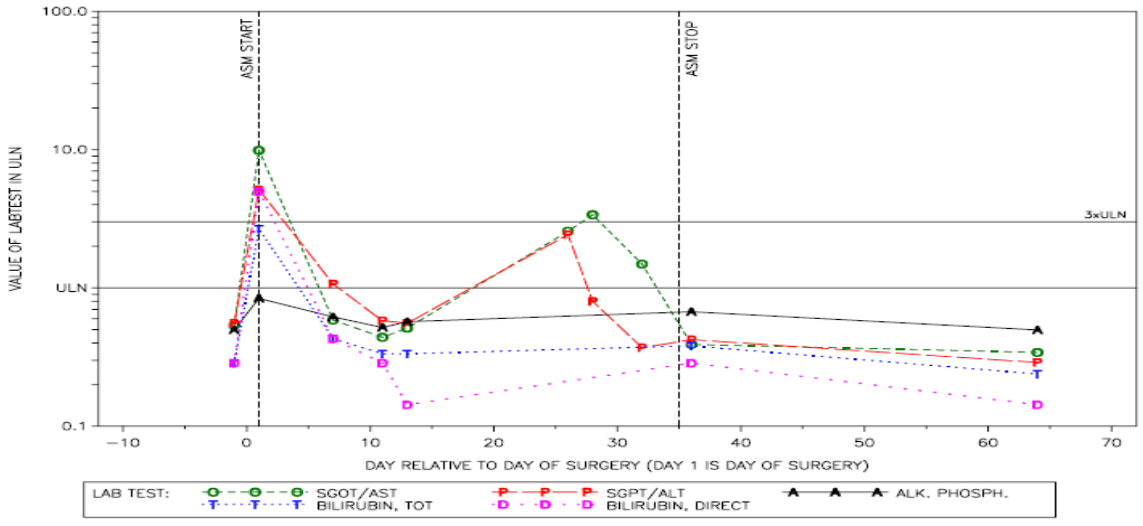
This 83 year old man had a medical history of polyp resection (1990), colectomy and colostomy (1996), prostate adenoma resection (1996), cholecystectomy (1996), vertigo ongoing, and deafness ongoing.

A primary hip arthroplasty (right side) due to osteoarthritis was performed on (b) (6) There were no known complications during surgery. The subject received rivaroxaban from (b) (6) Elevated transaminases were reported as non-serious events for the day of surgery prior to active rivaroxaban treatment ((b) (6), with ALT>5xULN, AST>8xULN, TB>2xULN, and GGT >5 x ULN. ALT/AST/TB resolved while study drug continued. There was a re-elevation in ALT/AST (ALT>2 xULN and AST>2xULN) on (b) (6) that normalized on (b) (6) based on local lab. The subject completed rivaroxaban treatment and the treatment was stopped on (b) (6) All those hepatic enzyme elevations resolved by (b) (6)

The investigator considered these events on (b) (6) as not related to study drug but the second period events on (b) (6) as related to study drug.

No other adverse events were reported.

The Liver Advisory Panel Evaluation concluded that an alternative explanation of the LFT elevations was the surgery. Causality was excluded.



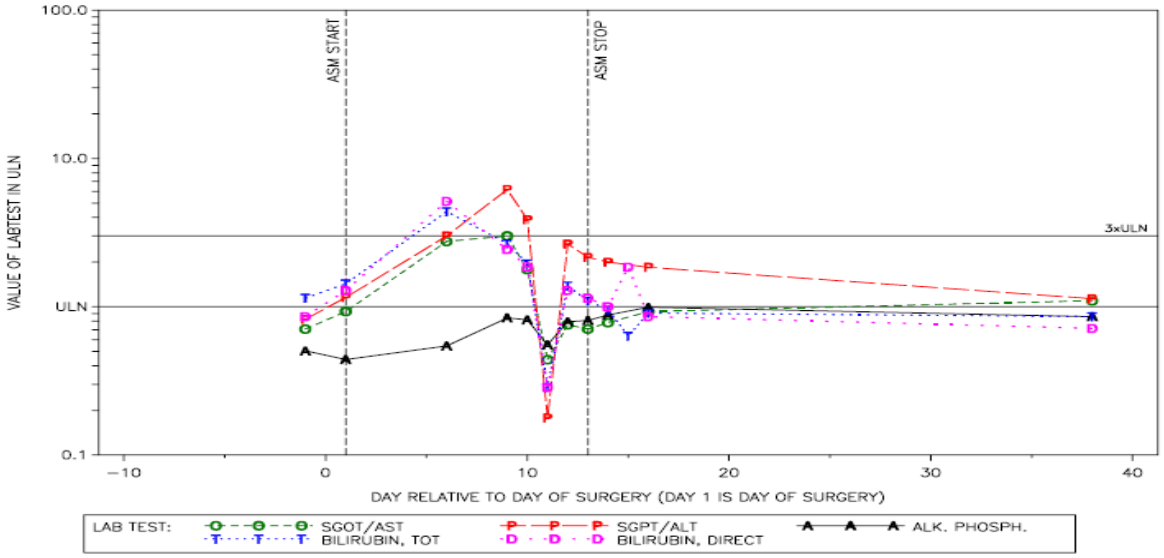
11354-18003-4018

This was a 49 year old white woman with a medical history of dislocation of left hip (1958), dysplastic arthritis of the left hip (2001-2006), appendectomy (2002), and electro-resection of cervix (2003).

A primary hip arthroplasty (left side) due to dysplastic arthritis was performed on (b) (6). The subject started rivaroxaban on (b) (6) Elevated levels of liver enzymes and bilirubin were found on (b) (6) and peaked on (b) (6) with ALT>5xULN, AST>2xULN, and TB>2xULN. The study drug treatment was discontinued due to thrombocythemia on (b) (6). ALT/AST were resolving after study drug was stopped. ALT/AST were close to normal and TB>1.5xULN on (b) (6)). No further LFT values were available. The investigator regarded these events as not related to the study drug.

No other reported adverse events except thrombocythemia.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11357-54001-7029

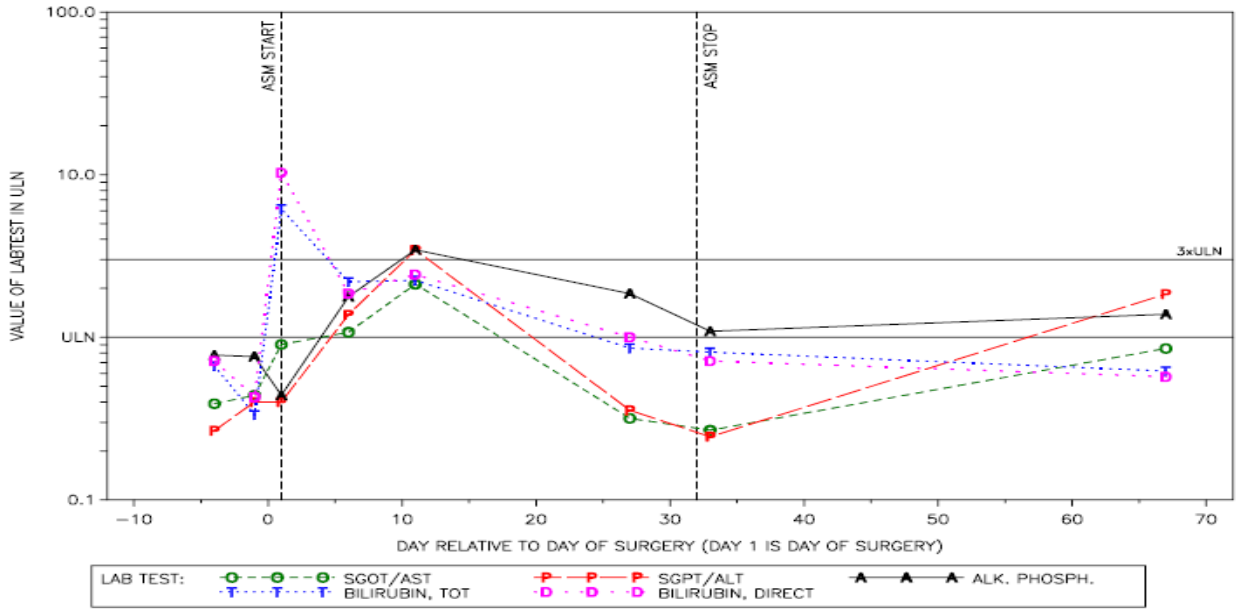
This 32 year old Asian male had a medical history of pulmonary tuberculosis (1996), and ankylosing and spondylitis (1996).

The subject was admitted for total hip replacement surgery under general anesthesia on (b) (6). On the same day he had started to receive BAY 59-7939 10 mg o.d. On (b) (6) the total bilirubin of the subject was reported as more than 6-fold upper limit of normal value. It decreased gradually while on study drug. Subject had elevations of ALT/AST on (b) (6) which peaked on (b) (6) (ALT>3xULN and AST>2xULN). Gluthion (1.200 mg, p.o. from (b) (6) was administered to the subject for liver protection. ALT/AST resolved by (b) (6)) while study drug continued. The subject completed Rivaroxaban treatment and the treatment was stopped on (b) (6). ALT increased >1.5xULN again on (b) (6) and no further LFT values were available.

Investigator considered these events as not related to study drug.

Other reported adverse events included mild productive cough from 20 Aug 2006 to 30 Aug 2006.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug for LFT elevations.



11357-55003-7007

This was a 52 year old Asian male with no significant medical history.

On [redacted] (b) (6) the subject had total hip replacement surgery under general anesthesia. On the same day he started rivaroxaban 10 mg o.d. p.o. The subject did not receive blood transfusion after surgery.

The subject had normal LFTs at baseline and mild elevations of ALT/AST/GGT on 12 Feb 2007 [redacted] (b) (6) and 13 Feb 2007 [redacted] (b) (6)). On 20 Feb 2007 [redacted] (b) (6) AST was normal and ALT/GGT remained slightly elevated. The last dose of rivaroxaban was on 15 Mar 2007. Marked elevations of ALT/AST/TB were noted on 16 Mar 2007 [redacted] (b) (6) (ALT>10xULN, AST>10xULN, and TB>3xULN). The subject reported nausea, dark urine, and weakness for 1 week [redacted] (b) (6)). Subject was hospitalized on [redacted] (b) (6) with hepatomegaly, jaundice, and vomiting. The subject was treated by the remedial therapy including Vitamin B complex, pulverized curcuma roots (herb), and lecithin. On [redacted] (b) (6), laboratory test for HbsAg was performed and the result was negative. On [redacted] (b) (6) ultrasonography showed no abnormality of liver, gall bladder and spleen. On [redacted] (b) (6), the condition of the subject was improved, infusion was stopped and subject only received vitamin B complex (1 capsule/day). [redacted] (b) (6) the subject was discharged. Elevations of liver enzymes gradually resolved over the time and ALT/AST/TB all normalized on 13 Apr 2007 (Day 65).

Hepatitis serology was performed on the retention samples of blood drawn at the time of each study visit. Blood samples from [redacted] (b) (6) showed HCV-Ab non-reactive and Blood samples from [redacted] (b) (6) showed HCV-

Ab positive. Quantitative PCR showed HCV-RNA positive from blood samples collected on [redacted] HCV concentration was 17.3 kIU/ml on [redacted] and 7.1 kIU/ml on [redacted] (reference: <10kIU/ml low virus concentration; >500 kIU/mL high virus concentration). HCV-RNA was negative (<0.01 kIU/ml) on [redacted] positive (26800 kIU/ml) on [redacted] and negative (<0.01kIU/ml) on [redacted]

Retention samples at baseline showed reactive IgG anti-HAV, HBsAg negative, positive HBs Ab, negative anti-HBc IgM and IgG, non-reactive anti-HCV.

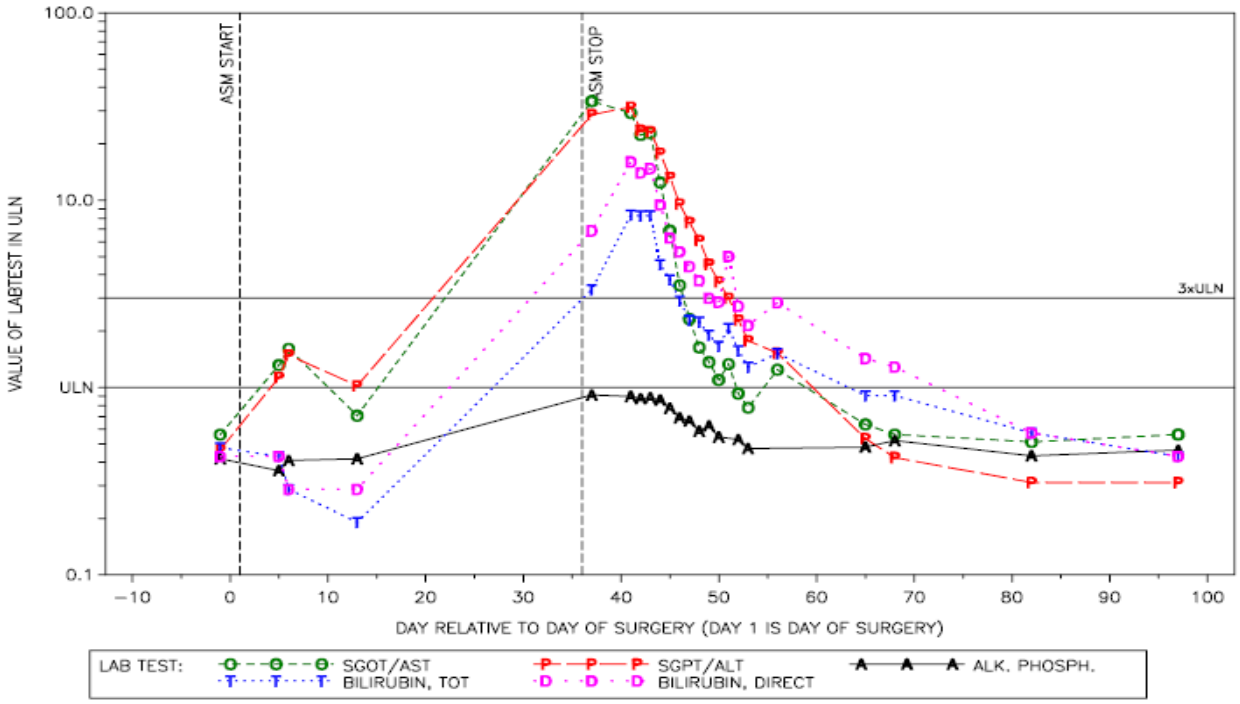
Blood sample on [redacted] showed positive for anti-HCV (Elisa and RIBA), anti-HBs, IgG-anti-HSV1, IgG anti-Toxoplasmosis, anti-Coxsackie (B2, B3, B4, B6).

Blood sample from [redacted]) showed quantitative and qualitative HCV-RNA-PCR (local lab) showed no virus detected.

The subject refused any further blood drawing reporting that he felt very well.

Investigator considered all above events as study drug related. Hepatitis C was not listed in the case report form.

The sponsor considered that these events were not study drug related and attributed these to Hepatitis C infection based serology and PCR tests.



11356-22001-6007

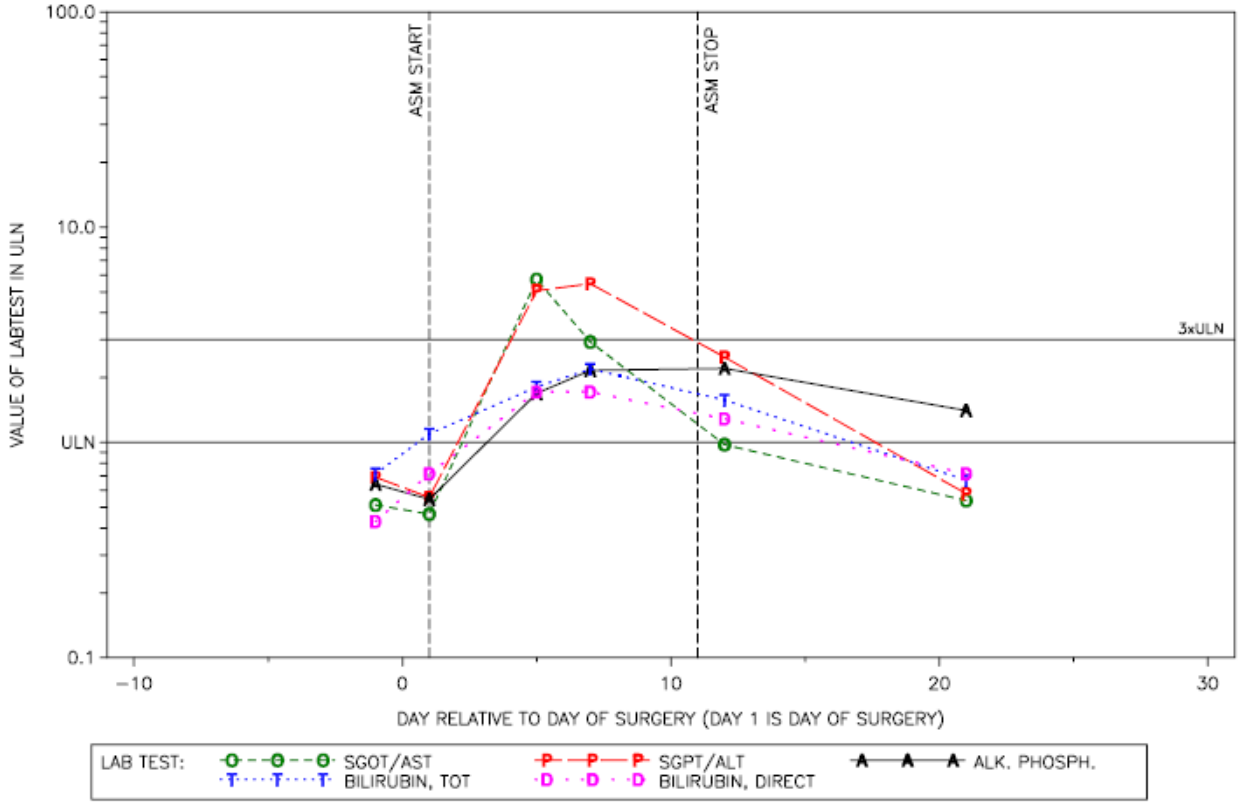
This 60 year old White female had medical history significant for venous insufficiency (2001) and hypertension (1996).

On (b) (6), the subject underwent a primary right knee arthroplasty under spinal anesthesia. On (b) (6)), the subject was noted to have an elevated ALT, AST, bilirubin, GGT, LDH, and alkaline phosphatase. ALT/AST/TB peaked on (b) (6) with ALT>5xULN, AST>3xULN and TB>2xULN. No therapy was given, and the subject was discharged from the hospital on (b) (6) The subject completed Rivaroxaban treatment for 11 days and the treatment stopped on 26 Mar 2006. The elevated AST was reported to have resolved on (b) (6)); the elevated ALT, bilirubin, GGT, LDH, and alkaline phosphatase were reported to have resolved on (b) (6)

Investigator considered these events as related to study drug.

Other reported adverse events included symptomatic proximal and distal DVT in right leg on (b) (6) .

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11356-26010-6008

This 55 year old White woman had medical history significant for hyperlipidemia (2003), osteoarthritis of the left knee (2002), left leg muscle spasms (2002), jaundice (1963) and cholecystectomy (1990).

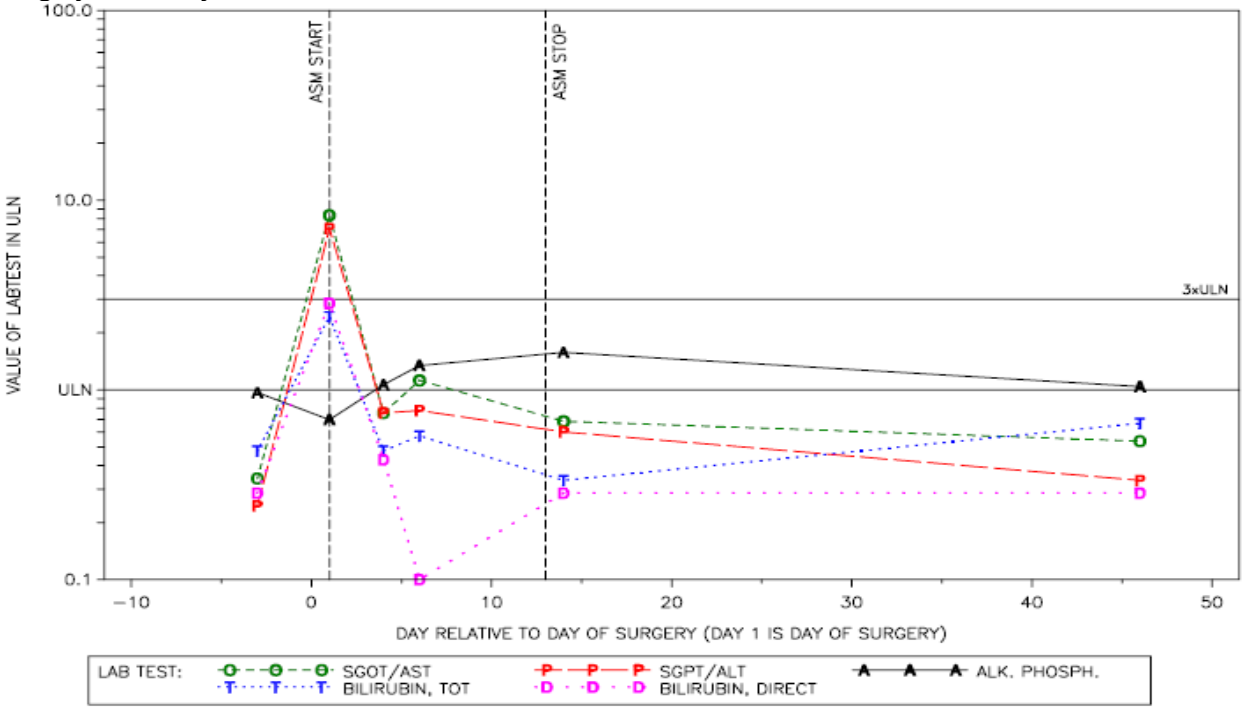
On (b) (6), the subject underwent a primary left knee arthroplasty with general anesthesia. On (b) (6) after surgery but before 1st dose of active rivaroxaban, the subject was noted to have an

elevated LFTs with ALT>5xULN, AST>8xULN and TB>2xULN. No action was taken, and these events were reported to have resolved on (b) (6)). The subject completed rivaroxaban treatment and the treatment was stopped on (b) (6). The subject was discharged from the hospital on (b) (6).

Investigator considered these events as not related to study drug.

No other adverse events were reported.

The Liver Advisory Panel Evaluation concluded that an alternative explanation of the elevations was the surgery. Causality was excluded.



11356-28018-6004

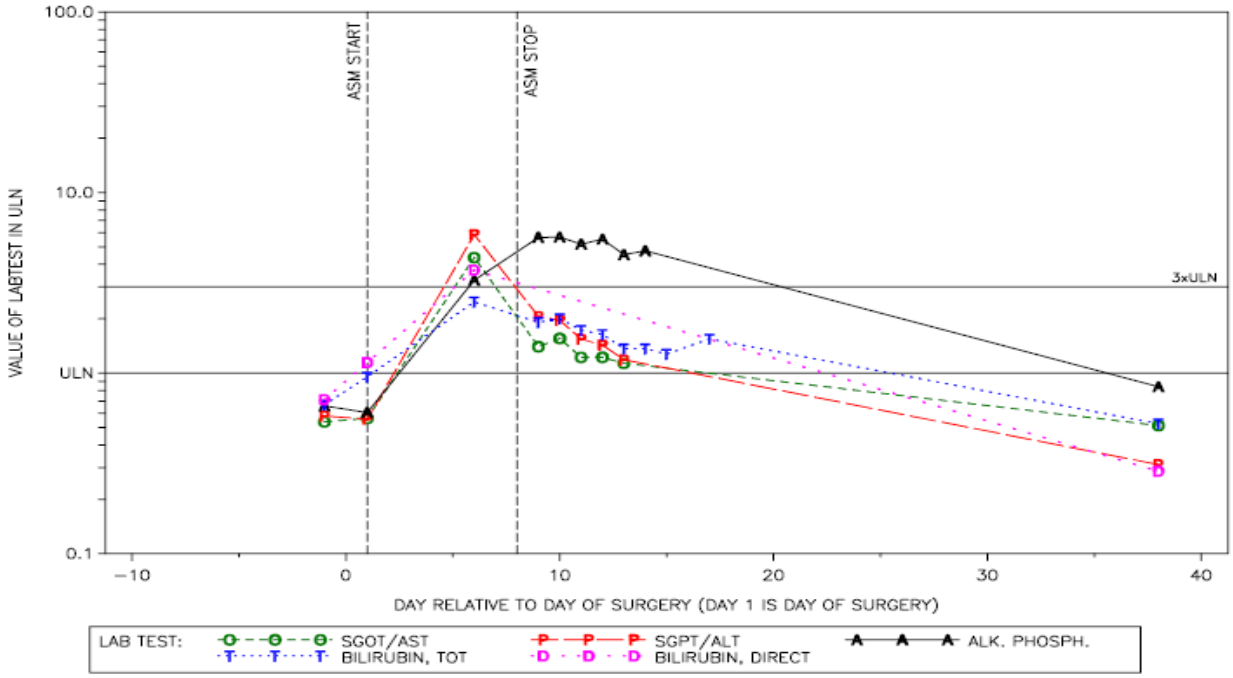
This 79 year old White male with medical history significant for prostatic hypertrophy (2006), bilateral inguinal hernia repair (1965), and osteoarthritis (ongoing, dates not reported).

On (b) (6), the subject underwent primary left knee arthroplasty with general anesthesia. On (b) (6), the subject was noted to have an elevated bilirubin, elevated AST, and elevated ALT. Each of these was reported as a serious adverse event. Study drug was permanently discontinued because of these events, with the last dose administered on (b) (6)), and the events were reported to have resolved on (b) (6)). The subject was discharged from the hospital on (b) (6).

Investigator considered these events as related to study drug.

No other adverse events were reported.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11355-60009-5028

This 72 year old Asian male had medical history significant for hypertension (2000) and coronary artery disease (1999). Alcohol consumption was reported as "abstinent."

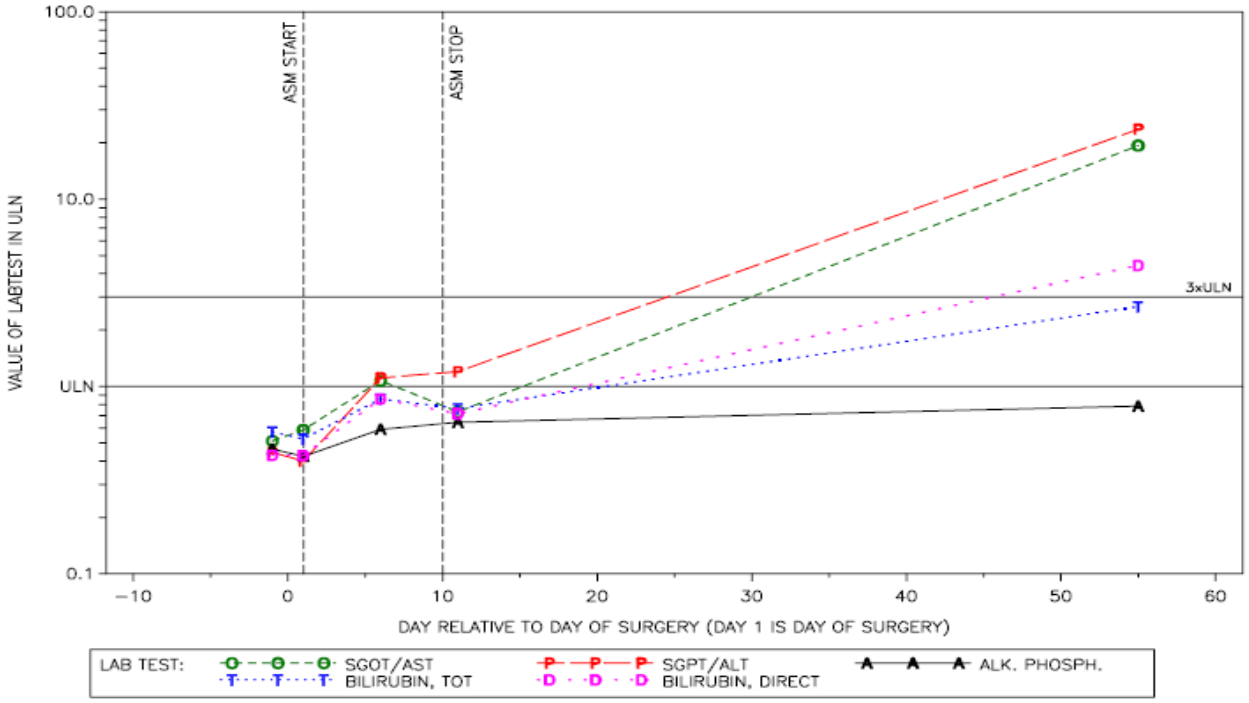
On [redacted] (b) (6), the subject underwent bilateral primary knee arthroplasties under spinal anesthesia. The subject was discharged on [redacted] (b) (6). The subject had mild elevation of ALT/AST on [redacted] (b) (6) and ALT on [redacted] (b) (6)). Marked elevations of ALT/AST/TB were on [redacted] (b) (6) with ALT>10xULN, AST>10xULN and TB>4xULN. No further LFT values were available. No action was taken. The outcome of the event was not reported due to insufficient follow-up. No further laboratory results were available.

According to the sponsor that follow-up of lab values was obtained after the results of RECORD 4 were unblinded showed that there was resolution of ALT on Day 72.

Investigator considered these events as not related to study drug.

No other adverse events were reported.

This case was assessed by the Liver Advisory Panel as possible related.



11355-90002-5011

This was a 57 year old Asian male with no significant medical history. Alcohol consumption was reported as "light."

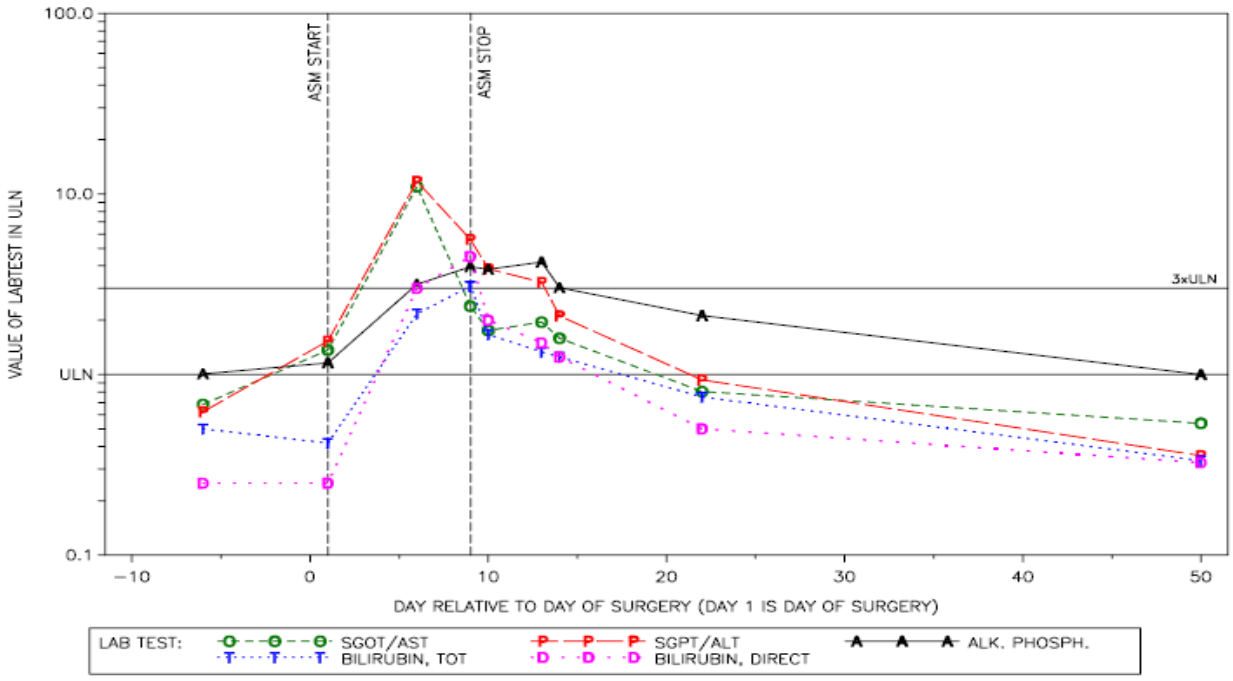
On [redacted] (b) (6) the subject underwent a primary right knee arthroplasty for osteoarthritis with spinal anesthesia.

On [redacted] (b) (6) postoperatively but before the first dose of study drug, the subject was noted to have a mild elevation of liver function tests. On [redacted] (b) (6) ALT/AST were peaked with ALT>10xULN, AST>10xULN and TB>3ULN. TB was elevated on [redacted] (b) (6) Study drug was discontinued permanently on [redacted] (b) (6). Study drug was discontinued permanently due to these events. ALT/AST/TB were back to normal on [redacted] (b) (6)). The subject was discharged from the hospital on [redacted] (b) (6).

Investigator considered these events as related to study drug.

No other adverse events were reported.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



Enoxaparin Group

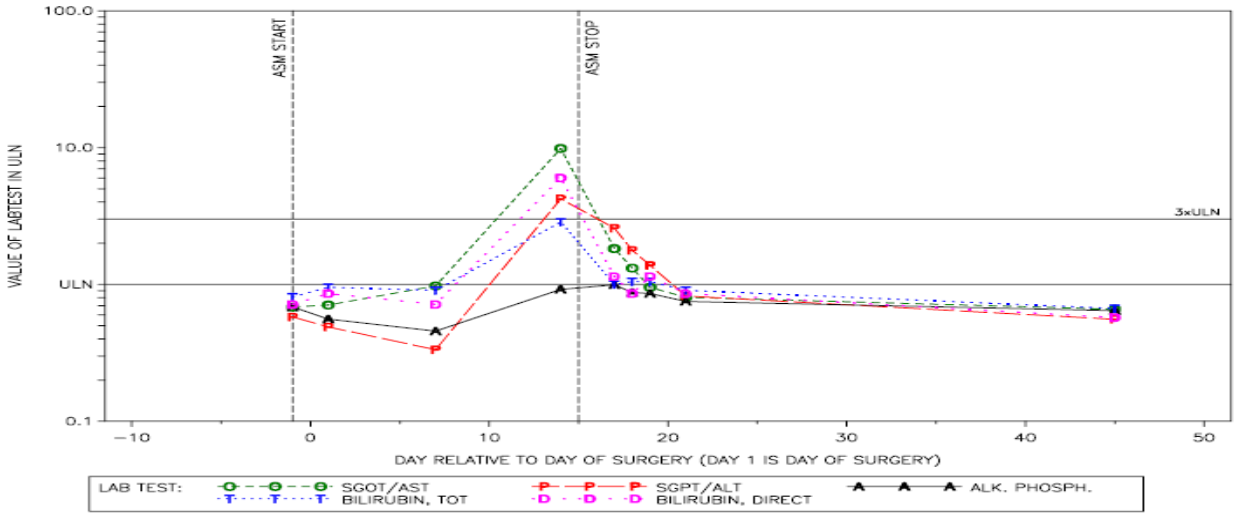
11354-18019-4037

This 74 year old White male had a medical history of right hand Dupuytren's contracture (1989-1994), brain circulatory insufficiency (1992), surgery for right hand Dupuytren's contracture (1994), coronary heart disease (1998), chronic gastritis (1998), esophageal hernia (1998), left hip osteoarthritis (1999-2006), and right hip osteoarthritis (2001).

A primary hip arthroplasty due to osteoarthritis was performed on [redacted] (b) (6). There were no known complications during surgery. On [redacted] (b) (6)) a moderate increase of liver enzymes was reported. Study drug treatment was discontinued on the same day. Liver enzymes returned to normal levels by [redacted] (b) (6).

The investigator considered this event as related to the study drug.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



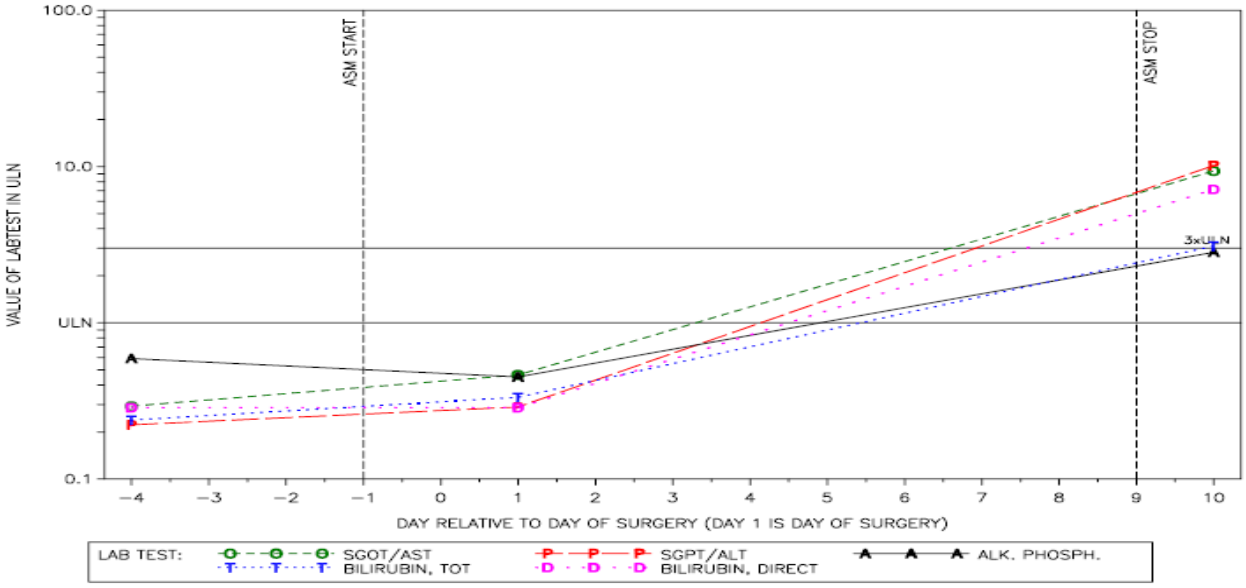
11357-12008-7009

This 85 year old White male had a medical history of right inguinal hernia repair, laser treatment of prostate gland, glaucoma right eye, hypertension and osteoarthritis.

The subject was admitted for total hip replacement surgery under spinal and epidural with indwelling catheter anesthesia on (b) (6). The day before, he had started to receive enoxaparin 40 mg o.d. s.c. On (b) (6) the subject developed symptoms of feeling cold, raised pulse and diarrhea, and was hospitalized. The event was treated with cefuroxime and metronidazole. On (b) (6), subcutaneous study medication was withdrawn. On (b) (6), acute cholecystitis was diagnosed with elevations of bilirubin, AST, ALT, and GGT. An abdomen CT was reported as showing gallstones within a non distended, thin walled gall bladder. There was no gross dilatation of the common bile duct. On (b) (6) the subject was discharged from hospital. The outcome was resolved with comment "ERCP to be performed as outpatient". The subject declined to attend any further follow appointments.

The investigator attributed elevated liver enzymes to cholecystitis as not related to the study drug.

The Liver Advisory Panel Evaluation concluded that causality of study drug was excluded.



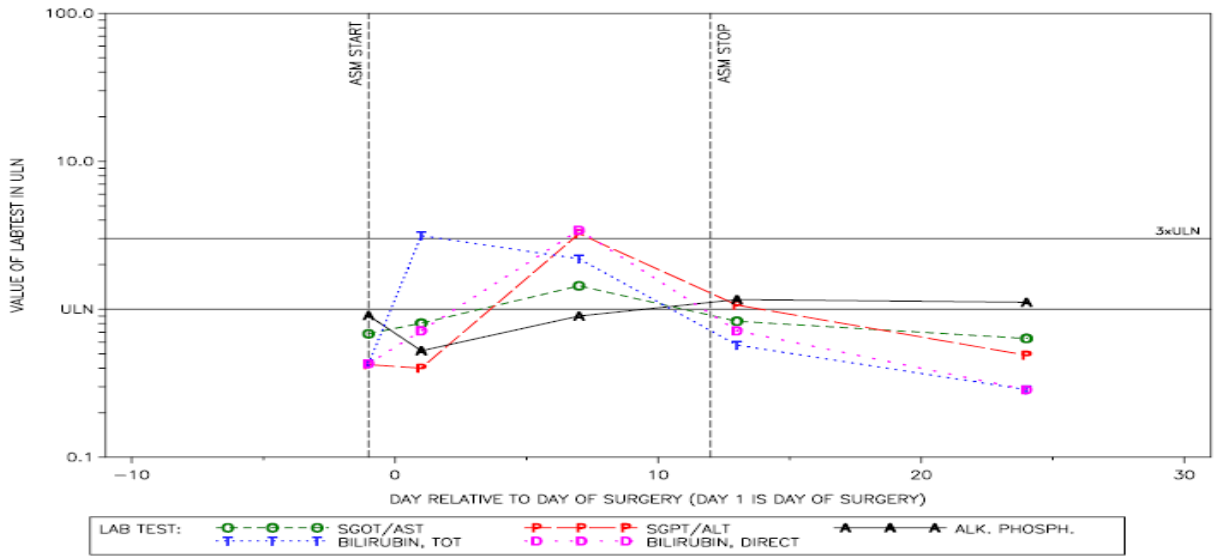
11357-48005-7034

This 64 year old female had medical history of rheumatoid arthritis, bladder surgery and hysterectomy.

The subject was admitted for total hip replacement surgery under spinal anesthesia on (b) (6). The day before she had started to receive enoxaparin 40 mg o.d. s.c. On (b) (6), the (b) (4) lab showed a Total Bilirubin > 3 xULN with normal ALT. On (b) (6) ALT/TB both elevated with ALT >3 xULN and TB >2 xULN. On (b) (6)), the study drug was discontinued. On (b) (6), the subject presented a complete normalization of ALT and Bilirubin values, after local and central retests.

The investigator considered this event as related to the study drug.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11357-60006-7001

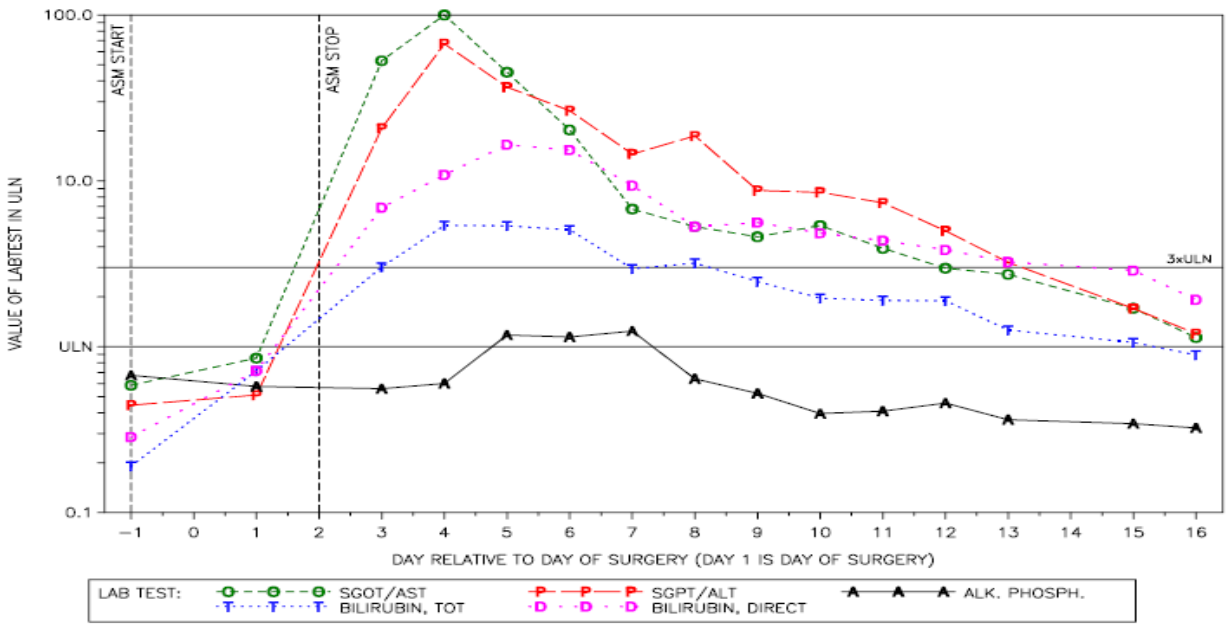
This 40 year old female had medical history of caesarean section surgery twice (1994 and 2001), tubal ligation (2001) and osteoarthritis of hips (since 2006).

The subject was admitted for total hip replacement surgery under general anesthesia on (b) (6). The day before, she had started to receive enoxaparin 40mg o.d. s.c.

On (b) (6), during surgery, intraoperative blood loss was 800 mL and 2 units of blood were transfused. On (b) (6) subject's blood pressure was low (90/60 mmHg) with decreased urine output and was treated with i.v. crystalloids (Ringer lactate and normal saline). Hypotension and acute renal failure were reported. On (b) (6) she was started on Dopamine to treat the hypotension. The study drug was permanently discontinued due to these events. On (b) (6)), local laboratory showed elevation of ALT/AST/TB. On (b) (6) liver enzymes rose further with ALT- 1030 IU/L and AST - 5440 IU/L. On (b) (6) ALT was 1060 IU/L and AST -750 IU/L. LFTs were gradually resolved and close to normal on (b) (6).

The investigator considered elevated liver enzymes as not related to the study drug.

The Liver Advisory Panel Evaluation concluded that the causality of study drug was excluded.



11355-14001-5020

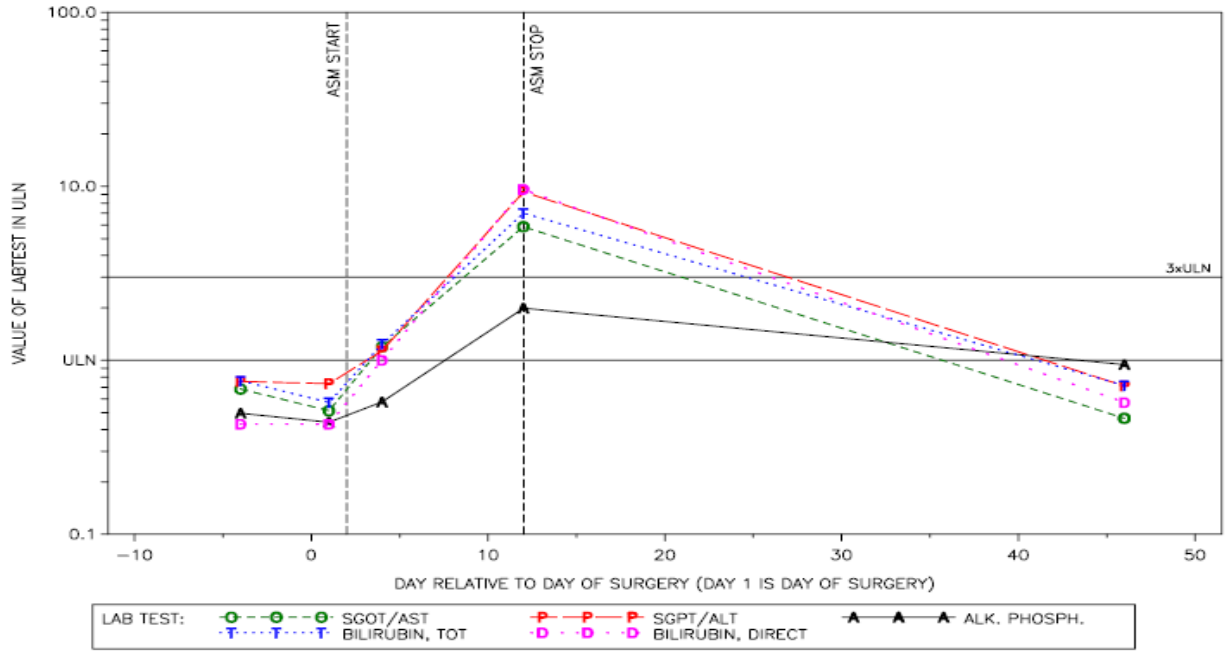
This 56 year old male had medical history significant for hypertension (2001), osteoarthritis of the left knee (2005), right knee arthroplasty (2005), gait instability (2005), moderate alcohol use, and hypercholesterolemia (2001).

On [redacted] (b) (6), the subject underwent a primary left knee arthroplasty for osteoarthritis under general anesthesia. The day before, she had started to receive enoxaparin 40mg o.d. s.c.

On [redacted] (b) (6) the subject was hospitalized for nausea, vomiting, diarrhea, and yellow skin, and a serious adverse event of elevated liver enzymes was reported. The elevated liver enzymes were repeated and monitored over the next several days. The subject was not able to complete an ERCP (endoscopic retrograde cholangiopancreatography) on [redacted] (b) (6) [redacted], so that an MCRP (magnetic resonance choloangiopancreatography) diagnostic procedure was performed on the same day. Results of the MRCP are not available. On [redacted] (b) (6) a cholecystectomy was performed for cholelithiasis and total obstruction of the common bile duct. He was discharged from the hospital on [redacted] (b) (6). LFT normalized on [redacted] (b) (6)

The investigator considered that elevated liver enzymes as not related to the study drug.

The Liver Advisory Panel Evaluation concluded that causality of study drug was excluded.



11355-14020-5027

This 75 year old man had medical history significant for benign prostatic hypertrophy (2006); asthma (1999); myocardial infarction and cataract surgery (1992); cardiac catheterization (1992); hypertension, type II diabetes, hypercholesterolemia and coronary artery disease (1992); left hernia repair (1963); tonsillectomy and adenoidectomy (1943); and penicillin allergy (dates not reported). Alcohol consumption was reported as "abstinent."

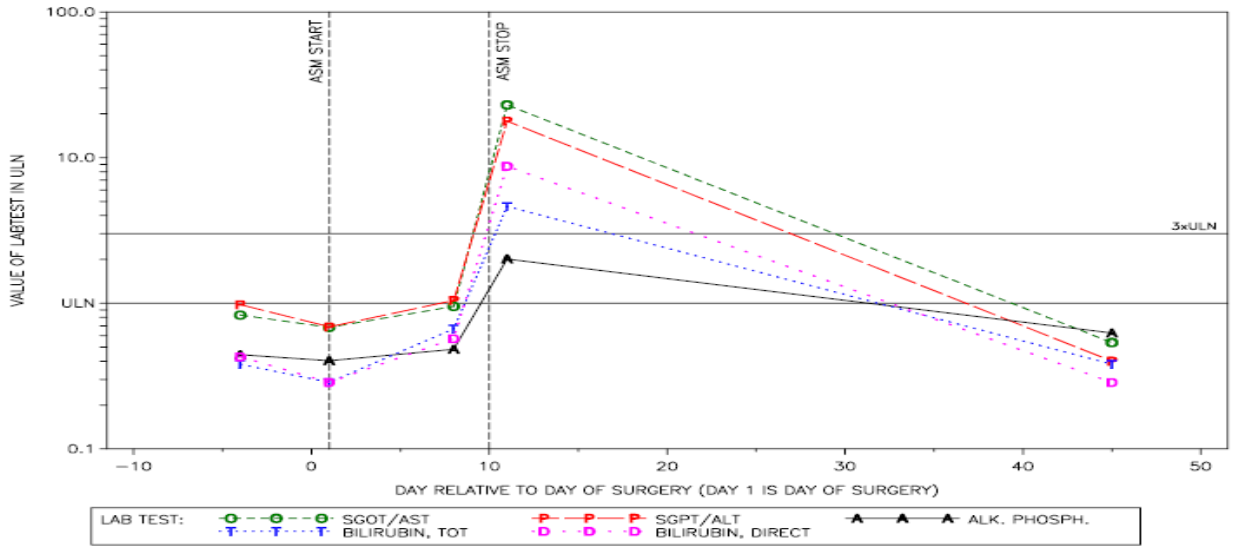
On (b) (6), the subject underwent a primary left knee arthroplasty under general anesthesia.

On (b) (6) the subject developed redness and swelling of the left (surgical) knee; he was diagnosed as having cellulitis of the left knee, and he was transferred from the rehabilitation center back to the hospital ((b) (6)). The subject was treated with antibiotics and the cellulitis was reported to have resolved on (b) (6).

On (b) (6) laboratory results revealed elevated liver enzymes. AST, ALT, and GGT values were > 8xULN and total bilirubin was > 4xULN. The subject was asymptomatic regarding liver failure. Study drug was discontinued permanently due to this event. The subject was discharged from the hospital on (b) (6) and the event was reported to have resolved on (b) (6)). Laboratory results showed normal LFTs on 26 Jul 2007.

The investigator considered this event as related to the study drug.

The Liver Advisory Panel Evaluation concluded that there was a possible causality of study drug.



11355-14020-5040

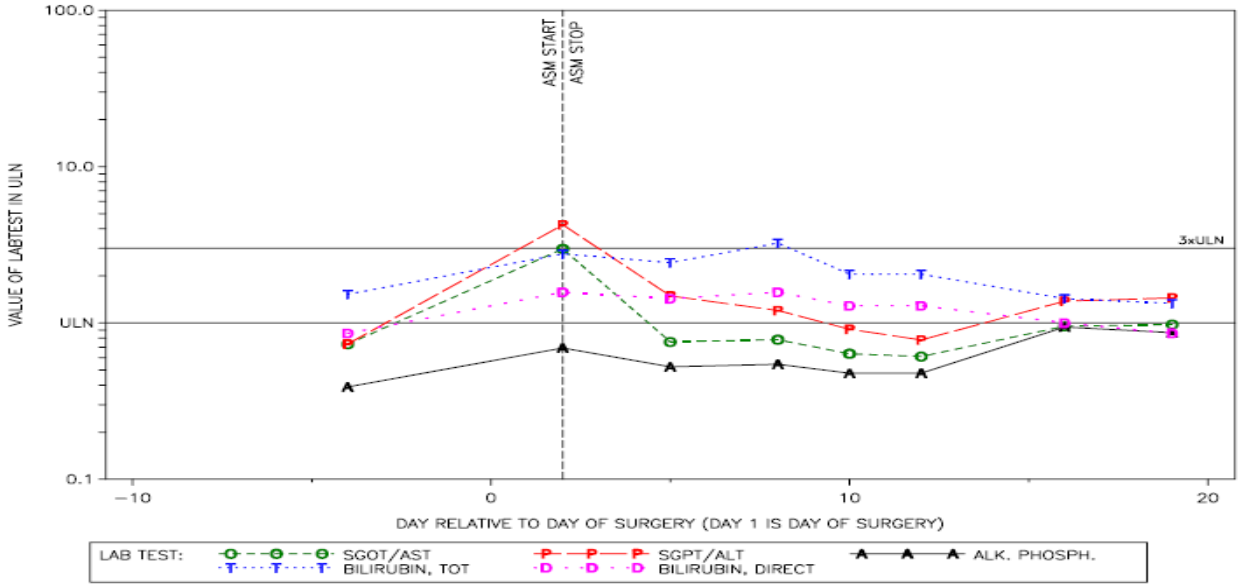
This 65 year old White male had medical history significant for hyperlipidemia, hypertension and osteoarthritis (2005), and right total knee replacement (2006). The following conditions were reported with unknown dates of onset and resolution: chronic leukopenia, arthrosclerosis of the carotid artery, tachycardia, colon polyps, status post endartectomy, onychomycosis, carpel tunnel release, cholecystectomy, and hiatal hernia repair. Alcohol consumption was reported as "moderate."

On (b) (6) the subject underwent primary left knee arthroplasty for osteoarthritis under spinal block anesthesia.

On (b) (6), central laboratory results showed normal liver function tests with the exception of total bilirubin and indirect bilirubin. On (b) (6)) elevated bilirubin and elevated ALT were reported. Study drug was discontinued permanently due to this event and the last dose was on 24 Jul 2007. The subject was discharged from the hospital on (b) (6). On (b) (6)), elevated liver functions were again reported as an adverse event. ALT was mild elevation on (b) (6) and normal on (b) (6) and mild elevation on (b) (6) AST normalized on (b) (6) No action was taken, and the event was reported to have resolved on (b) (6) TB was elevated before surgery and remained elevated on (b) (6). No further TB values were available.

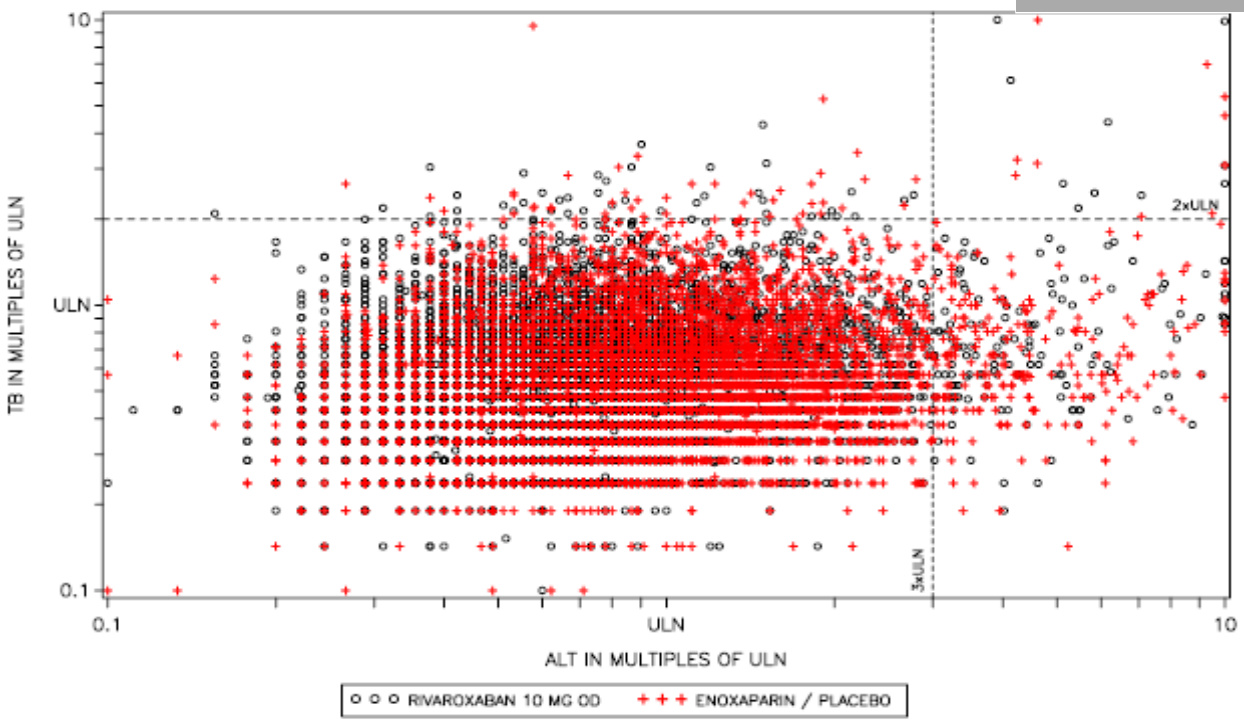
The investigator considered these events as not related to the study drug.

The Liver Advisory Panel Evaluation concluded that causality of study drug was excluded.



There was one additional enoxaparin subject (540017058) with non-concurrent ALT>3xULN (Day 11) with TB>2xULN (Day 2) based on central laboratory values. No rivaroxaban subject had non-concurrent ALT>3xULN with TB>2xULN based on central laboratory values. The following is plot of maximum of ALT with maximum TB in RECORD studies.

Figure 1-3: Scatter Plot of Maximum ALT Levels With Maximum Total Bilirubin Levels Occurring After Day 0 (Subjects Valid for the Safety Analysis in Pooled RECORD 1-4 Studies)



An additional one rivaroxaban subject and 2 enoxaparin subjects had non-concurrent ALT>3xULN with TB>2xULN based on local laboratory values. The 1 rivaroxaban subject and one enoxaparin subject had increased TB due to data entry error. Another enoxaparin subject with concurrent local laboratory elevations with a peak ALT of 309U/L (> 8X ULN) and TB of 2.09 mg /dL (>2X ULN) on Day 3 with decreases thereafter.

AST >3x ULN With a Concurrent Total Bilirubin >2x ULN

Five additional subjects (2 rivaroxaban and 3 enoxaparin) had an AST level >3x ULN concurrent with a total bilirubin level >2x ULN (see table below) without an ALT level >3x ULN. AST elevations occurred on Day 1 in both rivaroxaban subjects (i.e., prior to active rivaroxaban). In the enoxaparin group, 2 cases occurred on Day 1 and 1 case occurred on Day 8.

Individual Subjects with AST >3x ULN and Total Bilirubin >2x ULN in Phase 3 Studies (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

Study Drug Study/Subject ID Age/Sex	Day of Last Dose	Laboratory Values	Comments
Rivaroxaban			
11354-340054003 Figure 14.3.5/6.6.2A.2 79/female	34	AST = 188 U/L (Day 1) TB = 2.5 mg/dL (Day 1) DB = 1.0 mg/dL (Day 1)	Liver enzymes elevations began before first tablet administration; resolved while study drug continued
11357-540037018 Figure 14.3.5/6.6.2A.4 49/female	35	AST = 152 U/L (Day 1) TB = 3.9 mg/dL (Day 1) DB = 2.2 mg/dL (Day 1)	Liver enzymes elevations began before first tablet administration; resolving while study drug continued
Enoxaparin			
Figure 14.3.5/6.6.2A.1 78/female	32	AST = 177 U/L (Day 1) TB = 3.4 mg/dL (Day 1) DB = 1.9 mg/dL (Day 1)	Liver enzymes elevations resolved while study drug continued
11354-380034020 Figure 14.3.5/6.6.2A.3 69/male	31	AST = 291 U/L (Day 1) TB = 3.3 mg/dL (Day 1) DB = 1.1 mg/dL (Day 1)	Liver enzymes elevations resolving while study drug continued
11357-570017025 Figure 14.3.5/6.6.2A.5 75/female	11	AST = 125 U/L (Day 8) TB = 6.5 mg/dL (Day 8) DB = 3.8 mg/dL (Day 8)	Liver enzymes elevations resolved after discontinuation of study drug

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = direct bilirubin; TB = total bilirubin; ULN = upper limit of normal
Note: Day 1 = day of surgery and day of first tablet intake (active or dummy)

Hepatic Disorder Adverse Events

Adverse Events

A following table summarizes the post-baseline hepatic adverse events is RECORD studies. Overall, 290 subjects (4.7%) administered rivaroxaban and 400 subjects (6.5%) administered

enoxaparin reported a hepatic disorder adverse event. The vast majority of these adverse events reported by investigators in both treatment groups were adverse events due to abnormal liver-related laboratory tests. Of these, the most frequently reported events included the following: increased ALT, reported in 144 subjects (2.3%) given rivaroxaban and 200 subjects (3.2%) given enoxaparin; increased AST, reported in 116 subjects (1.9%) given rivaroxaban and 152 subjects (2.5%) given enoxaparin; and increased GGT, reported in 126 subjects (2.0%) given rivaroxaban and 183 subjects (3.0%) given enoxaparin. It was noted that more jaundice, ascites, and 1 hepatic failure were reported in the rivaroxaban group as compared to enoxaparin group.

Incidence of Postbaseline Hepatic Disorder Adverse Events[a]
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

MSSO Search Category MedDRA Preferred Term	Rivaroxaban (N = 6183)		Enoxaparin (N = 6200)	
Any below mentioned search category				
Any event	290	(4.69%)	400	(6.45%)
MSSO: Cholestasis and jaundice of hepatic origin				
Any event	5	(0.08%)	5	(0.08%)
Hyperbilirubinemia ~	1	(0.02%)	4	(0.06%)
Jaundice	4	(0.06%)	1	(0.02%)
Ocular icterus	1	(0.02%)	0	(0.00%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions				
Any event	6	(0.10%)	5	(0.08%)
Ascites ~	2	(0.03%)	0	(0.00%)
Hepatic failure	1	(0.02%)	0	(0.00%)
Hepatic lesion	0	(0.00%)	2	(0.03%)
Hepatic steatosis	3	(0.05%)	2	(0.03%)
Hepatotoxicity	0	(0.00%)	1	(0.02%)
Varices esophageal	1	(0.02%)	0	(0.00%)
MSSO: Hepatitis, non-infectious				
Any event	1	(0.02%)	2	(0.03%)
Cytolytic hepatitis	1	(0.02%)	0	(0.00%)
Hepatitis	0	(0.00%)	2	(0.03%)

MSSO: Liver infections				
Any event	1	(0.02%)	1	(0.02%)
Hepatitis B	1	(0.02%)	1	(0.02%)
MSSO: Liver neoplasms, benign				
Any event	1	(0.02%)	0	(0.00%)
Hepatic cyst	1	(0.02%)	0	(0.00%)
MSSO: Liver-related investigations, signs, and symptoms				
Any event	278	(4.50%)	395	(6.37%)
ALT abnormal	2	(0.03%)	1	(0.02%)
ALT increased	144	(2.33%)	200	(3.23%)
Ascites ~	2	(0.03%)	0	(0.00%)
AST abnormal	1	(0.02%)	1	(0.02%)
AST increased	116	(1.88%)	152	(2.45%)
Bilirubin conjugated increased	7	(0.11%)	6	(0.10%)
Blood Alk Phos abnormal	2	(0.03%)	0	(0.00%)
Blood Alk Phos increased	51	(0.82%)	81	(1.31%)
Blood bilirubin increased	23	(0.37%)	19	(0.31%)
Blood bilirubin unconjugated increased	8	(0.13%)	11	(0.18%)
GGT abnormal	1	(0.02%)	0	(0.00%)
GGT increased	126	(2.04%)	183	(2.95%)
Hepatic enzyme abnormal	2	(0.03%)	0	(0.00%)
Hepatic enzyme increased	20	(0.32%)	41	(0.66%)
Hepatic function abnormal	3	(0.05%)	5	(0.08%)
Hepatomegaly	1	(0.02%)	0	(0.00%)
Hyperbilirubinemia ~	1	(0.02%)	4	(0.06%)
Hypoalbuminemia	2	(0.03%)	8	(0.13%)
Liver function test abnormal	5	(0.08%)	12	(0.19%)
Liver palpable subcostal	0	(0.00%)	1	(0.02%)
Transaminases increased	2	(0.03%)	8	(0.13%)
MSSO: Possible liver-related coagulation and bleeding disturbances				
Any event	2	(0.03%)	1	(0.02%)
Protein S decreased	0	(0.00%)	1	(0.02%)
Prothrombin level decreased	1	(0.02%)	0	(0.00%)
Prothrombin time ratio decreased	1	(0.02%)	0	(0.00%)

[a] For MSSO search category Hepatic Disorders

Key: Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary of Regulatory Activities; MSSO = Maintenance and Support Service Organization

Note: All events after start of study medication are included regardless of onset relative to last dose of study medication

Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the event after the start of treatment

Note: Sorted alphabetically, first by search category then by MedDRA preferred term

Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories

Deaths

In the 4 Phase 3 RECORD studies, no subjects died from hepatic disorder adverse events.

Serious Adverse Events

Overall, 33 subjects (0.53%) administered rivaroxaban and 27 subjects (0.44%) administered enoxaparin had hepatic disorder serious adverse events (see table below)**.** The vast majority of these subjects (28 subjects [0.5%] receiving rivaroxaban and 26 subjects [0.4%] receiving enoxaparin) had adverse events that were increases in liver-related laboratory parameters. The most common hepatic disorder serious adverse event was increased ALT levels, seen in 17 subjects (0.3%) administered rivaroxaban and 14 subjects (0.2%) administered enoxaparin.

The subject with hepatic failure was a 72 year old White female who had a MI on Day 4 with hypotension. She developed acute renal and hepatic failure due to hypotension. AST/ALT levels were >10x ULN but TB was normal on Day 4. TB was slightly high on Day 6 and 7. All LFT abnormalities were resolved on Day 14. The investigator considered this event as not related. The LAP concluded that the causality of study drug was excluded.

The subject with ascites was an 81 year-old Asian male who was hospitalized on Day 40 for ascites and pleural effusions. LFTs were normal and albumin was 1.9 g/dL. This event was considered due to hypoproteinemia. The investigator considered this event as not related to the study drug.

Two subjects reported jaundice and both had bleeding events (wound of operation site and GI, respectively) and received transfusions. In both cases ALT levels were normal and TB was slightly higher with direct bilirubin >1.5 xULN. These two events were considered not related to the study drug by investigators. This event in both cases was resolved.

Incidence of Serious Post-baseline Hepatic Disorder Adverse Events[a]
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

MSSO Search Category MedDRA Preferred Term	Rivaroxaban (N = 6183)		Enoxaparin (N = 6200)	
Any below mentioned search category				
Any event	33	(0.53%)	27	(0.44%)
MSSO: Cholestasis and jaundice of hepatic origin				
Any event	3	(0.05%)	0	(0.00%)
Jaundice	3	(0.05%)	0	(0.00%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions				
Any event	2	(0.03%)	0	(0.00%)
Ascites ~	1	(0.02%)	0	(0.00%)
Hepatic failure	1	(0.02%)	0	(0.00%)
MSSO: Hepatitis, non-infectious				
Any event	0	(0.00%)	2	(0.03%)
Hepatitis	0	(0.00%)	2	(0.03%)
MSSO: Liver-related investigations, signs, and symptoms				
Any event	28	(0.45%)	26	(0.42%)
Alanine aminotransferase abnormal	2	(0.03%)	0	(0.00%)
Alanine aminotransferase increased	17	(0.27%)	14	(0.23%)
Ascites ~	1	(0.02%)	0	(0.00%)
Aspartate aminotransferase increased	5	(0.08%)	7	(0.11%)
Bilirubin conjugated increased	1	(0.02%)	0	(0.00%)
Blood alkaline phosphatase increased	0	(0.00%)	1	(0.02%)
Blood bilirubin increased	5	(0.08%)	4	(0.06%)
Gamma-glutamyltransferase abnormal	1	(0.02%)	0	(0.00%)
Gamma-glutamyltransferase increased	2	(0.03%)	4	(0.06%)
MSSO: Liver-related investigations, signs, and symptoms (continued)				
Hepatic enzyme increased	6	(0.10%)	7	(0.11%)
Liver function test abnormal	3	(0.05%)	1	(0.02%)
Transaminases increased	0	(0.00%)	2	(0.03%)
MSSO: Possible liver-related coagulation and bleeding disturbances				
Any event	1	(0.02%)	0	(0.00%)
Prothrombin time ratio decreased	1	(0.02%)	0	(0.00%)

[a] For MSSO search category Hepatic Disorders

Key: MedDRA = Medical Dictionary of Regulatory Activities; MSSO = Maintenance and Support Service Organization

Note: All events after start of study medication are included regardless of onset relative to last dose of study medication

Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the event after the start of treatment

Note: Sorted alphabetically, first by search category then by MedDRA preferred term

Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories

Adverse Events Leading to Discontinuation of Study Medication

Overall, 12 subjects (0.2%) receiving rivaroxaban and 17 subjects (0.3%) receiving enoxaparin in the RECORD studies experienced a hepatic disorder adverse event that led to permanent discontinuation of study medication (see Table below). The majority were discontinuations due to liver-related laboratory abnormalities, occurring in 10 subjects (0.2%) receiving rivaroxaban compared with 16 subjects (0.3%) receiving enoxaparin.

Incidence of Hepatic Disorder Adverse Events[a]
Resulting in Permanent Discontinuation of Study Medication
(Subjects Valid for Safety in Pooled RECORD 1-4 Studies)

MSSO Search Category MedDRA Preferred Term	Rivaroxaban (N = 6183)		Enoxaparin (N = 6200)	
Any below mentioned search category				
Any event	12	(0.19%)	17	(0.27%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions				
Any event	1	(0.02%)	0	(0.00%)
Hepatic failure	1	(0.02%)	0	(0.00%)
MSSO: Hepatitis, non-infectious				
Any event	1	(0.02%)	1	(0.02%)
Cytolytic hepatitis	1	(0.02%)	0	(0.00%)
Hepatitis	0	(0.00%)	1	(0.02%)
MSSO: Liver infections				
Any event	0	(0.00%)	1	(0.02%)
Hepatitis B	0	(0.00%)	1	(0.02%)
MSSO: Liver-related investigations, signs, and symptoms				
Any event	10	(0.16%)	16	(0.26%)
Alanine aminotransferase increased	7	(0.11%)	7	(0.11%)
Aspartate aminotransferase increased	3	(0.05%)	2	(0.03%)
Bilirubin conjugated increased	1	(0.02%)	2	(0.03%)
Blood alkaline phosphatase abnormal	1	(0.02%)	0	(0.00%)
Blood alkaline phosphatase increased	0	(0.00%)	1	(0.02%)
Blood bilirubin increased	1	(0.02%)	6	(0.10%)
Blood bilirubin unconjugated increased	0	(0.00%)	1	(0.02%)
Gamma-glutamyltransferase abnormal	1	(0.02%)	0	(0.00%)
Gamma-glutamyltransferase increased	2	(0.03%)	3	(0.05%)
Hepatic enzyme increased	1	(0.02%)	3	(0.05%)
Liver function test abnormal	2	(0.03%)	2	(0.03%)
Transaminases increased	0	(0.00%)	2	(0.03%)

[a] For MSSO search category Hepatic Disorders
Key: MedDRA = Medical Dictionary of Regulatory Activities; MSSO = Maintenance and Support Service Organization
Note: All events after start of study medication are included regardless of onset relative to last dose of study medication
Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the event resulting in permanent disc. of study drug
Note: Sorted alphabetically, first by search category then by MedDRA preferred term

7.3.4.4.2 Phase 2 Clinical Studies

7.3.4.4.2.1 VTE Prophylaxis Studies (Studies 10942, 10944, 10945, and 11527)

Abnormal Liver-related Laboratory Values

The incidence of liver-related laboratory abnormalities (defined as any elevation > 3x ULN occurring after surgery with pre-surgery as the baseline value) is presented by dose of study drug in the following table. Over the 12-fold total daily dose range evaluated in these Phase 2 studies, there does not appear to be a consistent dose-dependent increase in the incidence of selected liver-related laboratory abnormalities.

Incidence of Selected Laboratory Abnormalities After Surgery Start with Presurgery Baseline by Dose of Study Drug in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)

Laboratory	Rivaroxaban Total Daily Dose						Total	
Abnormality >3x ULN	5 mg	10 mg	20 mg	30 mg	40 mg	60 mg	RIVA	ENOX
ALT	19/425 (4.5%)	24/439 (5.5%)	16/434 (3.7%)	13/221 (5.9%)	24/432 (5.6%)	11/211 (5.2%)	107/2162 (4.9%)	38/533 (7.1%)
AST	18/425 (4.2%)	24/440 (5.5%)	24/431 (5.6%)	10/218 (4.6%)	21/427 (4.9%)	20/210 (9.5%)	117/2151 (5.4%)	34/ 532 (6.4%)
Total bilirubin	0/350 (0.0%)	1/362 (0.3%)	1/365 (0.3%)	1/131 (0.8%)	2/354 (0.6%)	1/138 (0.7%)	6/1700 (0.4%)	0/379 (0.0%)
ALK PHOS	2/425 (0.5%)	5/442 (1.1%)	2/435 (0.5%)	2/219 (0.9%)	1/434 (0.2%)	1/210 (0.5%)	13/2165 (0.6%)	2/538 (0.4%)
GGT	29/421 (6.9%)	40/430 (9.3%)	38/422 (9.0%)	21/217 (9.7%)	45/420 (10.7%)	17/197 (8.6%)	190/2107 (9.0%)	52/523 (9.9%)

[a] Subcutaneous enoxaparin (40 mg od) was administered in Studies 10942, 10944,and 11527; subcutaneous enoxaparin (30 mg bid) was administered in Study 10945.

Key: ALK PHOS = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; ULN = upper limit of normal

Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the abnormality postbaseline.
at risk = # of subjects with readings pre and postbaseline who did not report abnormality at baseline.

Note: Highest value prior to start of surgery is used as baseline.

Note: Highest value after surgery is used as postbaseline.

Note: If available, even measurements taken more than 7 days after end of treatment are considered here.

The incidence of liver-related laboratory abnormalities at varying thresholds occurring after the start of surgery for all rivaroxaban doses pooled together is presented in the following table. The incidence of ALT levels >3x ULN was lower in subjects receiving rivaroxaban (4.9%) compared with enoxaparin (7.1%) but the incidence of ALT levels >8x ULN was slightly higher in subjects receiving rivaroxaban compared with enoxaparin. The incidence of AST levels >3x

ULN was lower in subjects administered rivaroxaban (5.4%) compared with enoxaparin (6.4%). However, at higher thresholds the incidence was slightly higher in the rivaroxaban group as compared to the enoxaparin group. The incidence of abnormalities in total bilirubin >3 xULN and ALK PHOS>3xULN was slightly higher in the rivaroxaban group compared with enoxaparin. GGT were generally comparable at varying thresholds.

Four of 1700 subjects (0.2%) administered rivaroxaban and 2 of 379 subjects (0.5%) administered enoxaparin had ALT levels >3x ULN concurrent with bilirubin levels >2x ULN. One subject in the rivaroxaban group was not included in the table below. This subject had marked LFT elevation 39 days after the study treatment. These subjects are discussed in detail later.

Five of 1700 subjects (0.3%) administered rivaroxaban and 2 of 379 subjects (0.5%) administered enoxaparin had AST levels >3x ULN concurrent with bilirubin levels >2x ULN.

Incidence of Selected Laboratory Abnormalities After Start of Surgery (with Presurgery as Baseline) in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)

Laboratory Variable	Rivaroxaban N=2232		Enoxaparin N=555	
ALT >3x ULN and total bilirubin >2x ULN	**3/1700**	**(0.2%)**	**2/379**	**(0.5%)**
ALT, n (%)				
>3x ULN	107/2162	(4.9%)	38/533	(7.1%)
>5x ULN	42/2164	(1.9%)	14/534	(2.6%)
>8x ULN	17/2164	(0.8%)	3/534	(0.6%)
>10x ULN	9/2164	(0.4%)	2/534	(0.4%)
AST >3x ULN and total bilirubin >2x ULN	**5/1700**	**(0.3%)**	**2/379**	**(0.5%)**
AST, n (%)				
>3x ULN	117/2151	(5.4%)	34/532	(6.4%)
>5x ULN	50/2152	(2.3%)	11/532	(2.1%)
>8x ULN	24/2152	(1.1%)	5/532	(0.9%)
>10x ULN	21/2152	(1.0%)	3/532	(0.6%)

Total bilirubin, n (%)[a]				
>2x ULN	30/1699	(1.8%)	8/378	(2.1%)
>3x ULN	6/1700	(0.4%)	0/379	(0.0%)
>5x ULN	0/1700	(0.0%)	0/379	(0.0%)
Alkaline phosphatase, n (%)				
>3x ULN	13/2165	(0.6%)	2/538	(0.4%)
>5x ULN	0/2166	(0.0%)	0/538	(0.0%)
GGT, n (%)				
>3x ULN	190/2107	(9.0%)	52/523	(9.9%)
>5x ULN	78/2144	(3.6%)	21/529	(4.0%)
>8x ULN	21/2156	(1.0%)	6/531	(1.1%)
>10x ULN	11/2156	(0.5%)	2/531	(0.4%)

[a] Total bilirubin was not measured in Study 10942.
Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; ULN = upper limit of normal
Note: Incidence calculated in the at-risk population of subjects with a pre-surgery laboratory measurement not showing the defined abnormality and at least one laboratory measurement after start of surgery.
Note: The subjects reported in higher threshold categories will not always be included in lower threshold categories because this analysis is based on a treatment emergent approach that excludes subjects with baseline abnormalities.
Note: If available, measurements taken more than 7 days after end of treatment are included.

Alanine Aminotransferase Elevations Over Time

Most subjects have peak ALT elevations that occur before Day 10 and subsequently return to baseline. In Studies 10942, 10944, and 10945, the protocol did not require assessments of laboratory tests at the 30-day follow-up visit. Consequently, some subjects discontinued from study drug with elevated ALT levels and incomplete laboratory follow-up.

ALT or AST >3x ULN With a Concurrent Total Bilirubin >2x ULN

Four subjects administered rivaroxaban and 2 subjects receiving enoxaparin reported ALT increases >3x ULN concurrent with total bilirubin levels >2x ULN. The following table summarizes the patient's information, outcomes and investigator's assessment.

One subject in the rivaroxaban group died subsequently and others had LFT normalized. All cases in the rivaroxaban group were considered to be related to study drug and all cases in the enoxaparin group were considered to be not related to the study drug by investigator. A Liver Advisory Panel (LAP) was not formally established to review hepatic disorder adverse events from Phase 2 VTE prophylaxis studies. However, the death case (10944-84008) was reviewed by LAP.

ALT >3x ULN Concurrent With TB>2x ULN Cases in Phase 2 VTE Prophylaxis Studies

Age/sex Race ID	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	Investigator/LAP Assessment
Rivaroxaban					
84/F White	9	2	ALT 387/ TB 4.7	Resolving while study drug continued.	Related / -

10945-102-102016					
78/F White 10945-111-111011	6	2	ALT 206 / TB 2.4	Resolving while study drug continued.	Related / -
68/M White 11527-71005	4	1	ALT 518/ TB 2.9	Resolved after study drug stopped. The study drug was discontinued permanently.	Related / unlikely by one LAP member and possible by another LAP member
79/F White 10944-84008	8	47	ALT 190/ TB18.3	Hospitalized for jaundice and nausea, loss appetite on Day 47 and died with liver failure on Day 127.	Related/Unlikely
Enoxaparin					
71/F White 10944-75006	9	1	ALT 119/ TB 2.3	Resolving while study drug continued.	Not related/ -
80/F White 10944-84001	7	1	ALT 579/ TB 2.6	Resolving on study drug continued. Cholecystolithiasis was found.	Not related/ -

The following is the patient's narrative:

Rivaroxaban Group

10945-102-102016

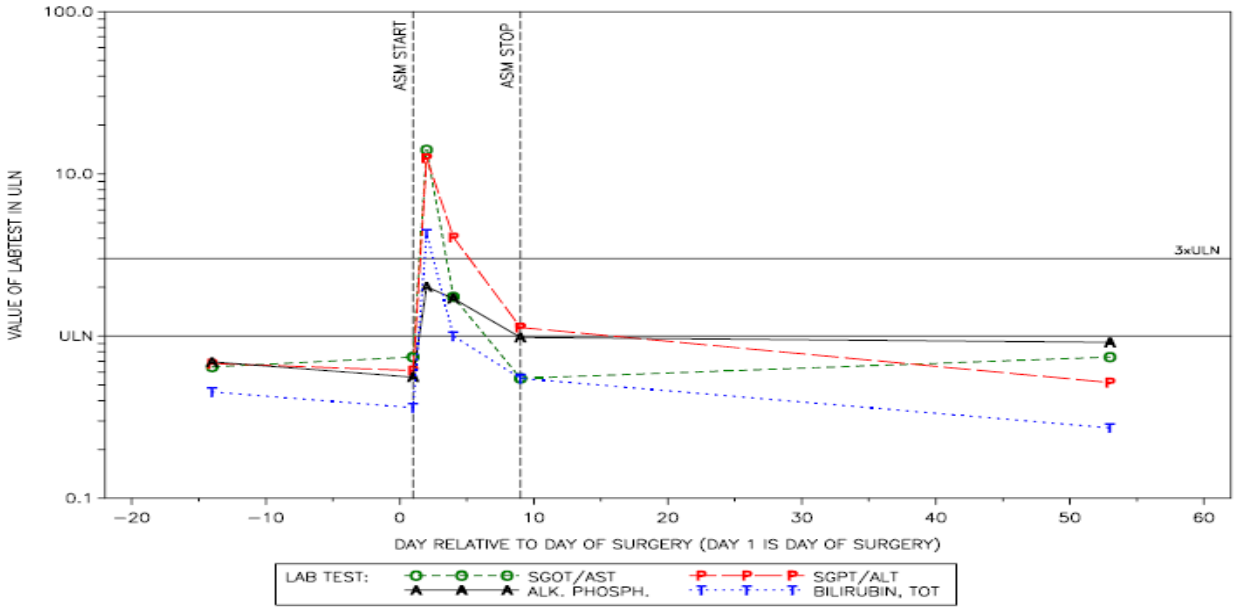
This 84-year-old White woman had a history of MI (1998) TIA (1998 & 2002), duodenal ulcer (1950), glaucoma (2003), diabetes mellitus (2003), right hip replacement (2003), titanium rods in neck (2000), cholecystectomy (1980), hypothyroidism (1994), hypercholesterolemia (1998), osteoarthritis, hypertension (1998) and CAD (1998).

The subject received rivaroxaban 20mg bid from 20 Jul 2004 to 28 Jul 2004 for 9 days.

On (b) (6) the total right knee replacement surgery was performed under spinal anesthesia. On (b) (6) the subject had elevated ALT, AST, GGT, alkaline phosphatase, billirubin, amylase and lipase. No action was taken and the abnormal values returned to normal or near normal on (b) (6) the subject was confused, agitated and appeared slightly jaundice. No

action was taken. The jaundice resolved on the same day, the agitation on (b) (6) and the confusion on (b) (6) The dose of study drug was not changed during the course of hospital treatment.

The investigator considered all these events as being related to study drug.



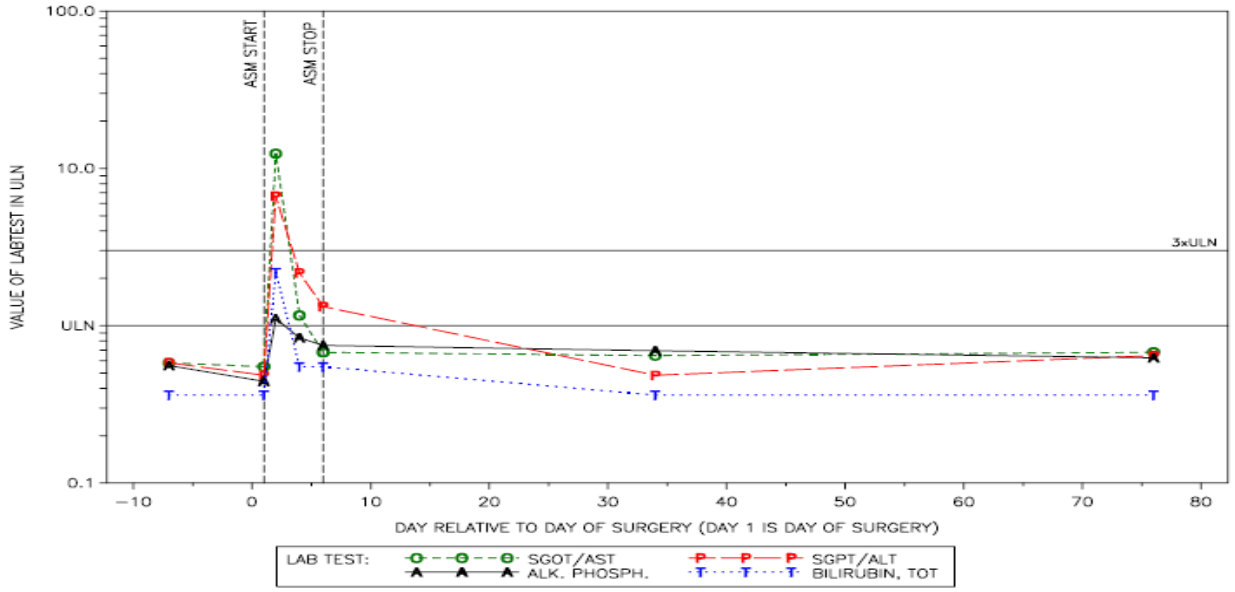
10945-111-111011

This 78-year-old White woman had a history of light alcohol consumption, smoking (1940 to 1990), osteoarthritis, chronic constipation, hypothyroidism, hypertension, GERD, hepatitis A (1959), right total hip replacement and nephrectomy on right kidney.

The subject received rivaroxaban 10mg bid from 9 Sep 2004 to 14 Sep 2004 for 6 days.

Total knee replacement surgery was performed on (b) (6) ALT, AST, GGT, LDH, alkaline phosphatase and billirubin were increased. All of the tests were moderate in severity and not serious except GGT which was considered as a serious event. The subject was retested at follow-up visit and GGT levels were slightly improved but still markedly elevated. All of the other liver function tests were transiently increased and were back to normal on (b) (6) the subject had vertigo and inability to concentrate, not requiring treatment. Both events resolved the next day. The dose of rivaroxaban was not changed, and the subject completed the study. On the follow-up visits of (b) (6), the result of GGT test was still increased, but gradually resolved towards normal.

The investigator considered abnormality of liver function laboratory tests to be related to the study drug.



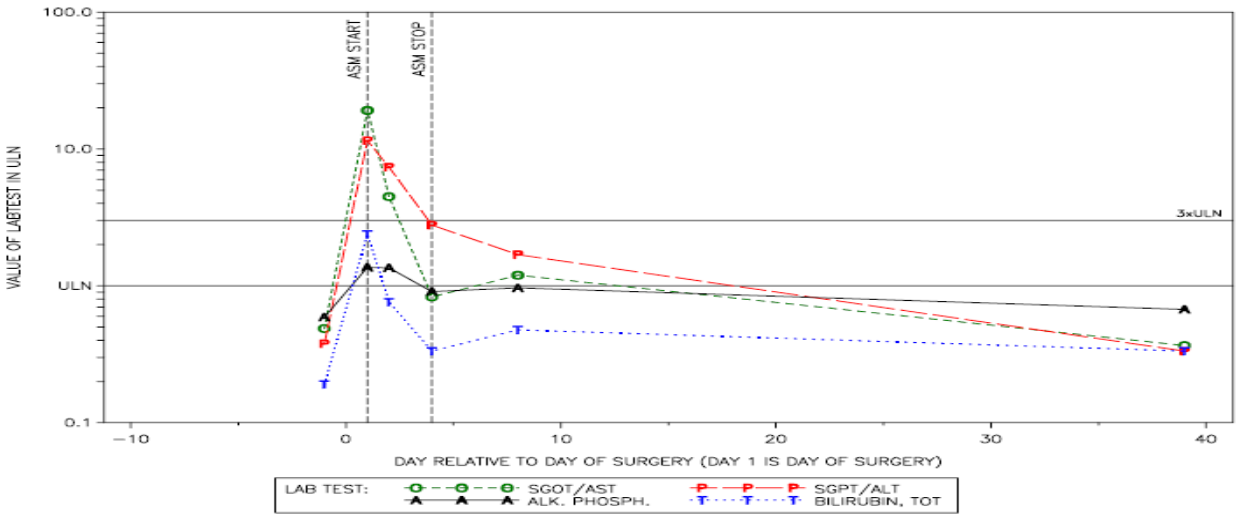
11527-71005

This 68 year old White male subject had medical history of appendectomy, cramps in legs, pleural plaque, hip pain, lactose intolerance, benign tumor in gallbladder, cholecystectomy and erectile dysfunction.

The subject received rivaroxaban [redacted] (b) (6).

Elective hip replacement was performed on [redacted] (b) (6). Elevated AST and ALT values were reported on 13 Dec 2004 (Day 1) with ALT>10 xULN, AST>10 x ULN, and TB>2xULN. GGT, ALK PHOS, and lipase also increased. The study drug was [redacted] (b) (6) and the events resolved without any treatment on [redacted] (b) (6)

The investigator considered elevated liver enzymes as related to the study drug.
The liver advisory panel considered as possible by one member and unlikely by another member.



10944-84008

This was a 79-year-old White female with a medical history of hypertension, cardiac insufficiency, compensated renal insufficiency, hyperuricemia, varicosis, coxarthrosis left side, cholecystolithiasis, hyperlipidemia and Parkinson's disease.

The subject received rivaroxaban from [redacted].

On [redacted], the patient underwent the elective hip replacement and received 1 unit heterologous packed cells in the evening. The patient suffered urinary tract infection on [redacted] which was treated with trimethoprim/sulfamethoxazoleand resolved on [redacted]. The subject was transferred to a rehabilitation facility from [redacted]). During rehabilitation tremor of right leg and right hand and mild distal edema of lower legs were reported and these improved after treatment.

On [redacted]) the patient went to her family doctor due to loss of appetite, weight loss, brown urine, nausea and vomiting. The subject was hospitalized. On admission increased liver enzymes (ALT 190, AST 504, GGT 566 U/L) and bilirubin (18.3 mg/dL) were found. Icterus of the sclerae and integrum was seen. Amlase and lipase were within the normal range. The abdomen was free of pain on pressure and there were no resistances palpable. Marked edema of lower legs and feet and tremor at rest were seen. No other pathological findings were reported.

On [redacted] ALT increased to 452 with AST of 178U/L, GGT of 538 U/L, and AP of 566 U/L. In the hepatitis serology (ELISA) only positive CMV-IgG- and EBV-IgG-antibodies were found.

On [redacted] abdominal ultrasound and ERCP with papillotomy, due to the fact that papillitis stenosans could not be excluded, were performed and except cholecystolithiasis no other abnormalities were found. After ERCP increased lipase (928 U/L) and amylase (151 U/L) was measured.

On [redacted] APTT was prolonged to 40.2 sec. and on [redacted] to 180 sec., on [redacted] APTT decreased to 29.8 sec. Prothrombin time was in normal range.

On [redacted] the liver biopsy showed mild to moderate fatty degeneration and lipofuscin enrichment, but no signs of inflammation.

The patient got several blood transfusions: 2 units on [redacted], 1 unit [redacted]
[redacted].

On [redacted] the condition of the patient worsened, the patient became somnolent. A cerebral CT showed marked cerebral atrophy and arteriosclerosis. Ammonia was 59 µg/dL (normal range 19-87). The lipase improved on [redacted] to 59 U/L.

During the hospital course liver-related parameters [ALT up to 639, AST to 550, GGT to 1987, AP to 2764 U/L on [redacted] bilirubin [highest value 54.6 mg/dL on [redacted] and inflammation parameter (CRP up to 12.4 mg/dL on [redacted] – normal range < 0.5) increased further.

On [redacted] (b) (6) phlegmonic cholecystitis with cholangitis was found in the sonography, which was resistant to antibiotic therapy. Additionally bronchopneumonia developed.

On [redacted] (b) (6) the patient died.

The autopsy was performed on [redacted] (b) (6). Post-mortem examination showed acute, necrotising pancreatitis with evidence of chronic or prior pancreatitis and acute cholecystitis due to cholecystolithiasis to be the cause of the jaundice. Findings also included bilateral bronchial pneumonia and bilateral pyelonephritis with septic spleen. Under the cause of death, it stated "Septic, cholemic heart and circulatory failure with bronchial pneumonia, acute cholecystitis and acute pancreatitis". Under Liver section, it stated "Hepatocytes already altered due to autolysis, portal fields not greatly enlarged, no glycogen nuclei, no signs of intrahepatic cholestasis."

The investigator considered the liver impairment and pancreatitis as related to the study drug.

The sponsor's Liver Advisory Meeting (2/17/2008) including 3 LAP members for RECORD studies concluded "Although this patient's cholestasis was unlikely related to rivaroxaban, this may be a drug-induced cholestasis. One potential candidate is Bactrim although temporal association cannot exclude rivaroxaban". Committee stated this is not a "liver death".

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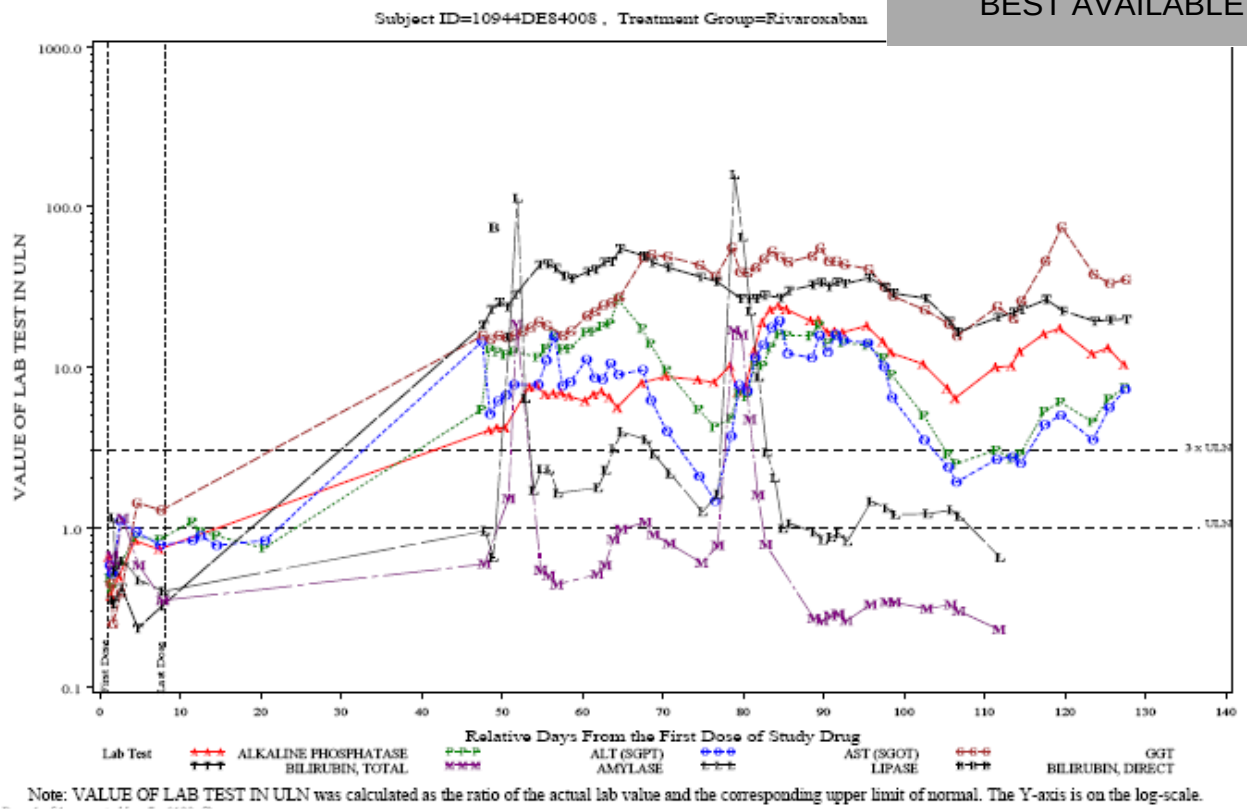


Note: VALUE OF LAB TEST IN ULN was calculated as the ratio of the actual lab value and the corresponding upper limit of normal. The Y-axis is on the log-scale.

Enoxaparin group

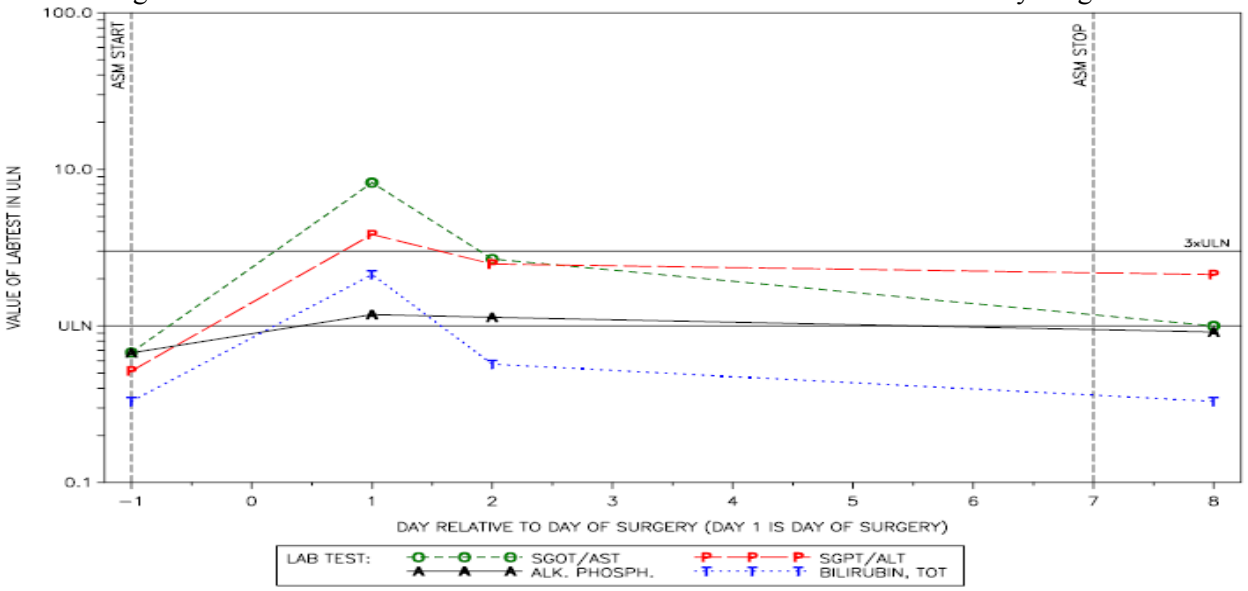
10944-75006

This 71-year old White female had a history of coxarthrosis left side (2001), phlegmona of hand (2002), cholecystectomy (1998) and fracture of right lower leg (1973).

The subject received Enoxaparin 40 mg od from [redacted] (b) (6) days.

Total hip replacement surgery took place on [redacted] (b) (6) until [redacted] (b) (6) [redacted] AST, ALT and total bilirubin increased. The next day the bilirubin value was in the normal range. At end of study drug therapy only GGT and ALT were slightly increased.

The investigator assessed the increase of AST and ALT as mild and not related to study drug.



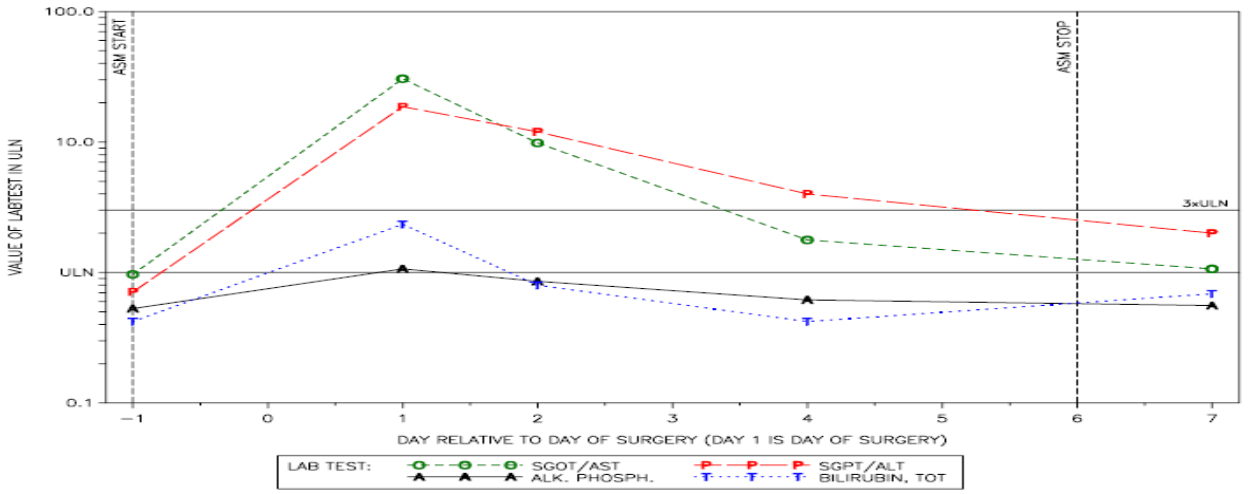
10944-84001

This 80 year old White female had medical history of coxarthrosis. Light alcohol consumption and non-smoking history were reported.

The subject received enoxaparin 40mg od [redacted] (b) (6)

Total elective hip replacement took place [redacted] (b) (6) abnormal liver parameters were reported (AST 947 U/L, ALT 579 U/L, GGT 288 U/L, LDH 1547 U/L, AP 111 U/L, bilirubin 2.6 mg/dL, amylase 176 U/L and lipase 227 U/L). An abdominal CT showed cholecystolithiasis. No action was taken. The values started to decrease on [redacted] (b) (6)).

The investigator considered this event as related to study drug and attributed this to cholelithiasis and post-anesthestic setting.



AST>3xULN concurrent with TB>2xULN

Two additional rivaroxaban subjects (in Study 10945) had AST levels >3x ULN concurrent with total bilirubin levels >2x ULN without ALT levels >3x ULN (see Table below); these events occurred on Day 4 and Day 6, respectively. Due to the design of the study protocol, which did not require laboratory testing at the follow-up visit, there was incomplete laboratory follow-up for both subjects. Subject 10945-102010 had elevated liver-related laboratory tests at the time of study drug discontinuation, and AST values for Subject 10945-131013 remained elevated at the time of study drug discontinuation.

Individual Subjects with AST >3x ULN and Total Bilirubin >2x ULN[a] in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)

Subject ID Age/Sex	Total Daily Dose	Day of Last Dose	Laboratory Values	Comments
Rivaroxaban				
10945/102010 Figure P/5.1.2.3 60/male	60 mg	Day 4	AST = 129 U/L (Day 6) TB = 4.1 mg/dL (Day 6)	Liver enzymes elevated after study drug discontinuation. Incomplete follow-up since labs not required by protocol.
10945/131013 Figure P/5.1.2.6 80/male	60 mg	Day 6	AST = 152 U/L (Day 2) TB = 3.8 mg/dL (Day 2)	AST elevations unresolved at the time of study drug discontinuation. Incomplete laboratory follow-up

[a] Without a corresponding increase in ALT levels >3x ULN
Key: AST = aspartate aminotransferase; TB = bilirubin; ULN = upper limit of normal
Note: Day 1 = day of surgery

Hepatic Disorder Adverse Events

Adverse Events

A summary table of treatment-emergent hepatic disorder adverse events is presented in following table**.** Overall, 168 subjects (7.5%) administered rivaroxaban and 52 subjects (9.4%) administered enoxaparin reported a hepatic disorder adverse event. The vast majority of these adverse events reported by investigators in both treatment groups were adverse events due to abnormal liver-related laboratory tests. The most frequently reported events included increases in the laboratory parameters of ALT, AST, and GGT.

Incidence of Treatment-Emergent Adverse Events in the MSSO Search Category 'Hepatic Disorders' in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)

MSSO Search Category/ MedDRA Preferred Term	Rivaroxaban Total (N=2232)		Enoxaparin (N=555)	
Any event	**168**	**(7.5%)**	**52**	**(9.4%)**
MSSO: Cholestasis and jaundice of hepatic origin				
Any event	4	(0.2%)	0	(0.0%)
Hyperbilirubinemia ~	2	(<0.1%)	0	(0.0%)
Jaundice	2	(<0.1%)	0	(0.0%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions				
Any event	1[a]	(<0.1%)	1	(0.2%)
Asterixis	0	(0.0%)	1	(0.2%)
Liver disorder	1[a]	(<0.1%)	0	(0.0%)
MSSO: Liver-related investigations, signs and symptoms				
Any event	165	(7.4%)	51	(9.2%)
Alanine aminotransferase increased	67	(3.0%)	25	(4.5%)
Aspartate aminotransferase increased	72	(3.2%)	25	(4.5%)
Blood alkaline phosphatase increased	20	(0.9%)	5	(0.9%)
Blood bilirubin increased	19	(0.9%)	0	(0.0%)
Gamma-glutamyltransferase increased	87	(3.9%)	27	(4.9%)
Hepatic enzyme increased	12	(0.5%)	7	(1.3%)
Hyperbilirubinemia ~	2	(<0.1%)	0	(0.0%)
Hypoalbuminemia	5	(0.2%)	0	(0.0%)
Liver function test abnormal	0	(0.0%)	2	(0.4%)
Transaminases increased	7	(0.3%)	4	(0.7%)
MSSO: Possible liver-related coagulation and bleeding disturbances				
Any event	1	(<0.1%)	0	(0.0%)
Coagulation Factor VII level decreased	1	(<0.1%)	0	(0.0%)
Prothrombin time ratio decreased	1	(<0.1%)	0	(0.0%)

[a] Subject 10944-84008 5.3.5.1.4-788

Key: MSSO = Maintenance and Support Services Organization
Note: All treatment-emergent events regardless of time after last study medication are included.
Note: Incidence = # of events / # at risk, where:
# of events = # of subjects reporting the event after the start of treatment
at risk = # of subjects in reference population
Note: Sorted alphabetically first by search category and then by MedDRA preferred term
Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories.

Deaths

One subject (10944-84008) died approximately (b) (6) after the last dose of rivaroxaban. This subject also met the criteria for ALT level >3x ULN concurrent with total bilirubin level >2x ULN. The patient's narrative has been presented in the early section in the ALT level >3x ULN concurrent with total bilirubin level >2x ULN.

Serious Adverse Events

Fourteen subjects (0.6%) administered rivaroxaban and 4 subjects (0.7%) administered enoxaparin had hepatic disorder serious adverse events (see Table below); the vast majority of subjects (12 of 14 subjects receiving rivaroxaban and 4 of 4 subjects receiving enoxaparin) had adverse events that were increases in liver-related laboratory parameters. In most cases, the liver-related laboratory parameter (e.g., ALT and AST) increased on the day of surgery (Day 1) or the first few days after surgery and was resolving or had completely resolved while study drug administration continued. In subjects where complete resolution had not occurred at the time of study drug discontinuation, follow-up laboratory tests at the 30-day follow-up visit showed normalization of ALT and AST. In 2 subjects administered rivaroxaban (Subjects 10945-113008 and 11527-67006) and 1 subject receiving enoxaparin (Subject 10944-84001), there was incomplete laboratory follow-up. As discussed earlier, laboratory assessments at the 30-day follow-up safety visit were not required and occurred at the discretion of the investigator.

In the table below, there was a serious adverse event with a preferred term of "liver disorder" that occurred in Subject 10944-84008; this subject is discussed in Section 2.1.2.2.

Incidence of Treatment-Emergent Serious Adverse Events in the MSSO Search Category 'Hepatic Disorders' in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)

MSSO Search Category/ MedDRA Preferred Term	Rivaroxaban Total (N=2232)	Enoxaparin (N=555)
Any event	**14 (0.6%)**	**4 (0.7%)**
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions		
Any event	1[a] (<0.1%)	0 (0.0%)
Liver disorder	1[a] (<0.1%)	0 (0.0%)
MSSO: Liver-related investigations, signs and symptoms		
Any event	12 (0.5%)	4 (0.7%)
Alanine aminotransferase increased	5 (0.2%)	0 (0.0%)
Aspartate aminotransferase increased	7 (0.3%)	2 (0.4%)
Blood alkaline phosphatase increased	2 (<0.1%)	0 (0.0%)
Gamma-glutamyltransferase increased	3 (0.1%)	0 (0.0%)
Hepatic enzyme increased	1 (<0.1%)	0 (0.0%)
Liver function test abnormal	0 (0.0%)	1 (0.2%)
Transaminases increased	1 (<0.1%)	1 (0.2%)
MSSO: Possible liver-related coagulation and bleeding disturbances		
Any event	1 (<0.1%)	0 (0.0%)
Coagulation factor VII level decreased	1 (<0.1%)	0 (0.0%)
Prothrombin time ratio decreased	1 (<0.1%)	0 (0.0%)

[a] Subject 10944-84008 5.3.5.1.4-788

Key: MedDRA = Medical Dictionary for Regulatory Activities; MSSO = Maintenance and Support Services Organization

Note: All treatment-emergent events regardless of time after last study medication are included.

Note: Incidence = # of events / # at risk, where:
# of events = # of subjects reporting the event after the start of treatment
at risk = # of subjects in reference population

Note: Sorted alphabetically first by search category and then by MedDRA preferred term

Adverse Events Leading to Study Discontinuation

Overall, 5 subjects (0.2%) administered rivaroxaban and 0 subjects administered enoxaparin had hepatic disorder adverse events leading to study discontinuation (see Table below). The most common events included increased ALT, AST, and increased hepatic enzymes.

Incidence of Hepatic Disorder Adverse Events Leading to Study Discontinuation in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)

MSSO Search Category/ MedDRA Preferred Term	Total Rivaroxaban (N=2232)		Enoxaparin (N=555)	
Any event	**5**	**(0.2%)**	**0**	**(0.0%)**
MSSO: Liver-related investigations, signs, and symptoms				
Any event	4	(0.2%)	0	(0.0%)
Alanine aminotransferase increased	1	(<0.1%)	0	(0.0%)
Aspartate aminotransferase increased	1	(<0.1%)	0	(0.0%)
Hepatic enzymes increased	3	(0.1%)	0	(0.0%)
MSSO: Possible liver-related coagulation and bleeding disturbances				
Any event	1	(<0.1%)	0	(0.0%)
Coagulation factor VII level decreased	1	(<0.1%)	0	(0.0%)
Prothrombin time ratio decreased	1	(<0.1%)	0	(0.0%)

Key: MedDRA = Medical Dictionary for Regulatory Activities; MSSO = Maintenance and Support Services Organization
Note: Incidence = # of events / # at risk, where:
# of events = # of subjects reporting the event resulting in permanent disc. of study drug
at risk = # of subjects in reference population
Note: Sorted alphabetically first by search category then by MedDRA preferred term

7.3.4.4.2.2 VTE Treatment Studies (Studies 11223 and 11528)

The Phase 2 DVT treatment studies consisted of 2 randomized, active controlled, parallel-group studies in subjects with an acute symptomatic deep vein thrombosis that was objectively confirmed. The scheduled duration of treatment in the Phase 2 DVT treatment studies was 84 days. The control group in both studies received initial treatment (first 5 to 7 days) with heparin (enoxaparin in Study 11223 and unfractionated heparin, tinzaparin, or enoxaparin in Study 11528) followed by a vitamin K antagonist (VKA) for the remainder of the 84-day duration. Subjects with transaminases ≥2x ULN were excluded from enrollment in these studies.

Summary of Liver-related Laboratory Values

A schedule of liver-related laboratory assessments in the 2 DVT treatment studies is provided in the following table**.** Day 1 laboratory measurements were obtained prior to study drug initiation in both studies.

Schedule of Liver-related Laboratory Assessments in Phase 2 Treatment Studies in Venous Thromboembolism

Study	Day 1	Day 5-7	Day 21	Day 43	Day 56	Day 84	Follow-up
11223	X	X	X		X	X	No
11528	X			X		X	Yes

Note: Post treatment follow-up laboratory tests were not required

The incidence of treatment-emergent, liver-related laboratory abnormalities at varying thresholds is presented in the following table**.** At most thresholds of liver-related laboratory abnormalities, the incidence of elevated ALT, AST, and GGT levels was lower in subjects receiving rivaroxaban compared with subjects receiving comparator. There were more events of total bilirubin levels >2x ULN and ALK PHOS levels >3x ULN in subjects administered rivaroxaban. The lower incidence of ALT, AST, and GGT >3x ULN in subjects administered rivaroxaban compared with heparin/VKA in the pooled analysis was primarily driven by Study 11223. In Study 11528, there were few events of ALT, AST, or GGT levels >3x ULN and the incidence of these abnormalities was comparable between the treatment groups.

There were 1 case of ALT and AST levels >3x ULN concurrent with a total bilirubin level >2x ULN in the Rivaroxaban group and no case in the heparin/VKA group. The one case in the rivaroxaban group subsequently died of liver failure. The patient narrative and detailed information are provided in later section.

Incidence of Treatment-emergent Liver-related Laboratory Abnormalities (All Postbaseline Measurements) in Phase 2 Treatment Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 11223 and 11528)

Laboratory Variable	Rivaroxaban N=883		Heparin/VKA N=263	
ALT >3x ULN and bilirubin >2x ULN	**1[a]/824**	**(0.1%)**	**0/235**	**(0%)**
ALT, n (%)				
>3x ULN	20/832	(2.4%)	26/238	(10.9%)
>5x ULN	5/834	(0.6%)	12/239	(5.0%)
>8x ULN	2/834	(0.2%)	4/239	(1.7%)
>10x ULN	1/834	(0.1%)	2/239	(0.8%)
AST >3x ULN and bilirubin >2x ULN	**1[a]/824**	**(0.1%)**	**0/235**	**(0%)**
AST, n (%)				
>3x ULN	10/827	(1.2%)	16/237	(6.8%)
>5x ULN	4/831	(0.5%)	4/238	(1.7%)
>8x ULN	2/831	(0.2%)	1/238	(0.4%)
>10x ULN	1/831	(0.1%)	0/238	(0.0%)
Total bilirubin, n (%)				
>2x ULN	3/824	(0.4%)	0/235	(0.0%)
>3x ULN	2/824	(0.2%)	0/235	(0.0%)
>5x ULN	1/824	(0.1%)	0/235	(0.0%)
>8x ULN	1/824	(0.1%)	0/235	(0.0%)
>10x ULN	1/824	(0.1%)	0/235	(0.0%)

Alkaline phosphatase, n (%)				
>3x ULN	4/829	(0.5%)	0/237	(0.0%)
>5x ULN	3/831	(0.4%)	1/238	(0.4%)
>8x ULN	0/833	(0.0%)	1/238	(0.4%)
>10x ULN	0/833	(0.0%)	1/238	(0.4%)
GGT, n (%)				
>3x ULN	23/805	(2.9%)	13/228	(5.7%)
>5x ULN	11/825	(1.3%)	9/237	(3.8%)
>8x ULN	6/828	(0.7%)	2/238	(0.8%)
>10x ULN	5/831	(0.6%)	0/238	(0.0%)

[a] Increased ALT and AST values seen in the same subject (11223-506006) 5.3.5.4.1-1211

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; ULN = upper limit of normal; VKA = vitamin K antagonist

Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the abnormality postbaseline.
at risk = # of subjects with readings pre and postbaseline who did not report abnormality at baseline.

Note: Postbaseline measurements taken more than 2 days after last intake of study medication are included

Note: The subjects reported in higher threshold categories will not always be included in lower threshold categories because this analysis is based on a treatment emergent approach that excludes subjects with baseline abnormalities.

Alanine Aminotransferase Elevations Over Time

A pooled analysis of the frequency of ALT > 3x ULN by time window is shown in Table below. The incidence of ALT levels >3x ULN was lower on rivaroxaban compared with heparin/VKA before Weeks 2. However, the incidence of ALT levels >3x ULN was high on Rivaroxaban compared with heparin/VKA after Day 35 (1.4% vs. 0.9%).

Frequency of ALT >3x ULN by Time Windows
(Subjects Valid for Safety in Studies 11223 and 11528)

	Rivaroxaban # of Events/# Evaluable (%)		Heparin/VKA # of Events/# Evaluable (%)	
Baseline	3/856	(0.4%)	2/250	(0.8%)
Weeks 1-2 (Days 2-18)	7/467	(1.5%)	23/126	(18.3%)
Weeks 3-4 (Days 19-35)	3/442	(0.7%)	1/117	(0.9%)
Weeks 6-8 (Days 36-69)	8/797	(1.0%)	1/230	(0.4%)
Weeks 12 (Days 70-91)	3/750	(0.4%)	0/227	(0.0%)
After Day 35[a]	11/805	(1.4%)	2/215	(0.9%)
After Day 91	2/413	(0.5%)	1/126	(0.8%)

[a] Calculated as the number of subjects with a laboratory abnormality after Day 35 relative to all subjects with normal measurement(s) prior to Day 35 and at least 1 measurement after Day 35

Key: ALT = alanine aminotransferase; Labs = laboratory results; ULN = upper limit of normal; VKA = vitamin K antagonist

Note: Subjects with normal baseline and at least 1 postbaseline measurement are at risk.

Note: Postbaseline measurements taken more than 2 days after last intake of study medication are included.

Kaplan Meier plots of the time to first ALT level >3x ULN in Study 11223 and Study 11528

are presented in the following Figures.

Figure 2-3: Cumulative Risk (Kaplan Meier) of First Laboratory Abnormality Versus Time After Start of Study Medication
Abnormality: ALT >3x ULN
(Subjects Valid for Safety in Study 11223)

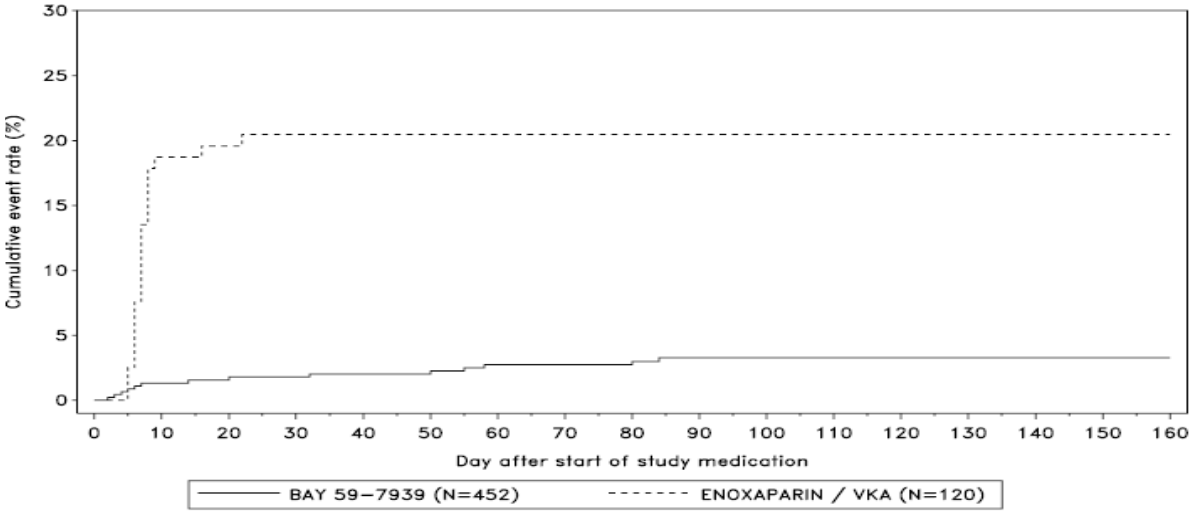
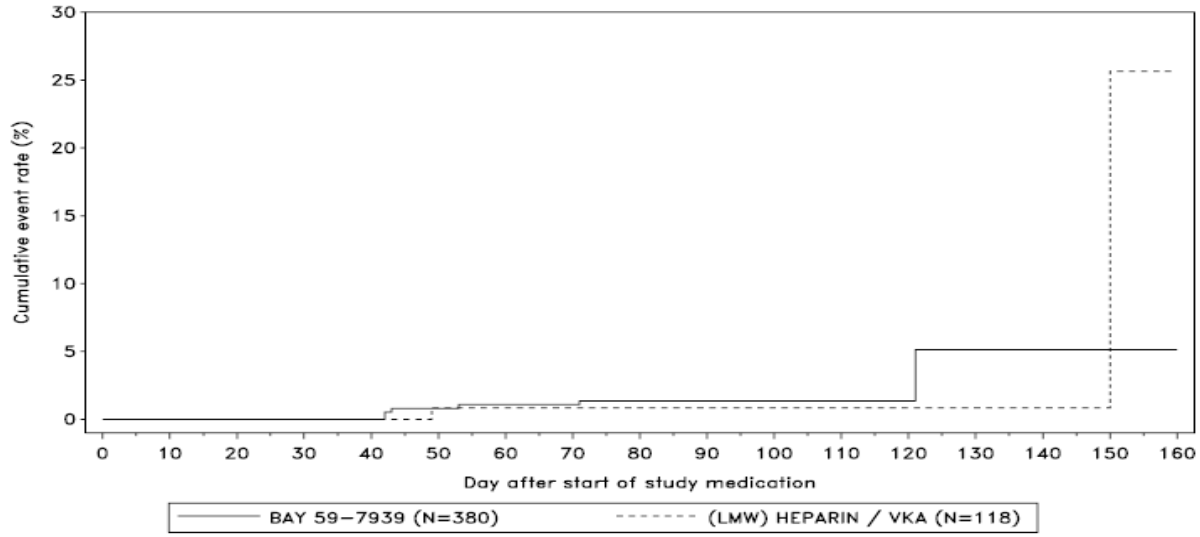


Figure 2-4: Cumulative Risk (Kaplan Meier) of First Laboratory Abnormality Versus Time After Start of Study Medication
Abnormality: ALT >3x ULN
(Subjects Valid for Safety in Study 11528)



The profile of the comparator arm (heparin/ VKA) is most notably different between the 2 studies and is considered due to the relatively intense laboratory sampling in Study 11223 occurring at a time when elevations in ALT are expected to occur on enoxaparin. In Study 11528, the relatively flat profile of the heparin/VKA arm through the first month reflects a lack of laboratory sampling at the time when elevations in ALT would be expected to occur. The profiles of time to first ALT level >3x ULN of the rivaroxaban arm in Studies 11223 and 11528 are comparable. In Study 11528, the time to first event comparison is considered primarily one

of rivaroxaban versus a VKA because the VKA was used after the first 5 to 7 days of heparin/LWMH.

In Study 11528, 2 cases of late occurring elevations in liver enzymes after the last dose of study drug were observed, 1 in each study group. Laboratory assessment was not required in the follow-up period (after study drug discontinuation), but it was at the discretion of the investigator. Based on available data, 1 event in 35 subjects receiving rivaroxaban and 1 event in 4 subjects receiving enoxaparin.

ALT or AST >3x ULN With a Concurrent Total Bilirubin >2x ULN

In Phase 2 studies in VTE treatment, there was 1 case of ALT and AST levels >3x ULN concurrent with a total bilirubin level >2x ULN in the Rivaroxaban group and none in the heparin/VKA group.

The subject (11223-506006) randomized to receive rivaroxaban had ALT and/or AST levels >3x ULN in conjunction with total bilirubin levels >2x ULN and died of liver failure after 48 days of treatment with rivaroxaban 40 mg once daily.

The following is the patient narrative.

This is a 72 year old female subject with a medical history of hypertension, diabetes mellitus, DVT (2004), uterine malignancy (uterine sarcoma stabilized) with lung and mediastinal metastases (2004), and subsequent hysterectomy with bilateral adnectomy (2004) and 6 cycles palliative chemotherapy (2005). During the chemotherapy in (b) (6) the subject got two transfusions on (b) (6). On 14 Apr 2005 no liver metastases, but cyst or pseudocyst of pancreas up to 20 mm of size, were seen in ultrasound.

The patient started BAY 59-7939 40 mg once daily on 05 May 2005 due to femoropopliteal thrombosis.

On 05 May 2005 prior to start of rivaroxaban, liver related tests were normal except slight increased GGT level. On 11 May 2005 (Day 7), ALT, AST, GGT and bilirubin levels were within normal limits.

On 24 May 2005 (b) (6) marked elevations of ALT (2477 U/L), AST (1544 U/L), GGT (537 U/L), bilirubin (2 mg/dL) and AP (304 U/L) were noted. The subject was febrile and had slight icterus. In ultrasound no abnormalities were found.

On 27 May 2005 (b) (6) rivaroxaban was discontinued permanently due to these events.
Serum protein electrophoresis showed: Albumin was 0.43 (normal range 0.53-0.65), alpha-1-globulin 0.069 (normal range 0.02-0.04), alpha-2-globulin 0.091 (normal range: 0.08-0.13), Beta-globulin 0.134 (normal range 0.09-0.16), gamma-globulin 0.163 (normal range 0.115-0.19) and albumin globulin 1.2. Alpha-1-globulin, acute phase protein was elevated.

On 30 May 2005 (b) (6) hepatitis serology showed: S-anti HAV IgM negative, S-anti HAV total 96.65 (normal<50), HBsAg 216.21 (normal <2), anti-HBs negative, HBeAg negative, anti-HCV negative. Ultrasound showed: liver no detectable lesions, gall bladder thickened wall, probable chronic cholecystitis, tumor can not be ruled out, intrahepatic bile ducts not enlarged, common bile duct slightly dilated, pancreas not enlarged, two round hypoechogenic structures of 10 and 21 mm size, similar

structure at caudal of pancreas of 11 mm size (retroperitoneal lymph nodes or pseudocysts?), 11 mm hypoechogenic structure of 1mm diameter at pancreas caput (head).

Routine investigation of the blood donation samples revealed that they were negative for HBsAg and anti-HCV-AB; no PCR testing performed in transfusion samples; no retention samples are available for further investigations; no further information on blood donation samples is available.

On 31 May 2005 (b) (6), CT showed: Liver no focal changes, no signs of dilatation of intra- and extrahepatic bile ducts. Gallbladder: low filling, suspected thickened wall, chronic cholecystitis can be ruled out. Pancreas: thin in all parts, distinct borders, no signs of expansion. No pathological enlarged lymph nodes in peripancreatic region or porta hepatic. In right subphrenic region calcified lymph node of 10mm diameter. Normal spleen and kidneys. Abdominal aorta: artherosclerotic changes. Spondylosis of thoracic and lumbar spine. Conclusion: no signs of cholelithiasis, suspected chronic cholecystitis, no signs of retroperitoneal lymphadenopathy.

On 03 Jun 2005 (b) (6) serology test showed: anti HBc IgM 3.2, anti HBe 65.34.The subject was transferred to the infection ward. Progression of icterus and development of liver failure was reported. No signs of encephalopathy were seen. The subject got following remedial therapy: Antibiotics because of fever accompanied with shivering, Essentiale® (essential phospholipids, vitamins), Transmetil® (ademetionine butanedisulfonate), Helicid® (omeprazole) and Aspegic® (acetylsalicylic acid). In addition following infusion solutions were given Nutramin® (aminoacid infusion solution), Plasmalyte® (electrolyte infusion) and glucose. As prophylaxis Dalacin® (clindamycin) and Ciprinol® (ciprofloxacin) from 29 May 2005 to 06 Jun 2005 were given. She got Fraxiparin® (nadroparin 0.3 mL) from 28 May 2005 to 21 Jun 2005.

On 04 Jun 2005 (b) (6), serum protein electrophoresis showed Albumin and alpha-2-globulin were slightly decreased and alpha-1-globulin and gamma-globulin increased.

On 08 Jun 2005 (b) (6), HBs Ag was 315.09, HBe Ag negative and anti-HBe 69.74 (normal <60). The diagnosis of acute hepatitis B was made based on serology tests– increase of HBs Ag titer, 3 fold increase of anti HBc IgM and negative HBeAg with only discrete increase of anti HBe antibodies.

In central laboratory the hepatitis serology was as following:

	05 May 2005 (day 1)	24 May 2005 (day 21)
HBs Ag	positive	positive
HBs Ab	0 UI/mL	0 UI/mL
HBc Ab (total)	negative	positive
HBc Ab IgM	NA	positive
HBe Ag	negative	negative
HBe AB	negative	negative

The subject had positive HBs Ag at baseline prior to the start of rivaroxaban.

On 18 Jun 2005 (b) (6) liver enzymes decreased, considered by the investigator as sign of liver failure. Icterus progressed and the subject died on (b) (6)) due to acute liver failure.

The following are liver-related test results:

Central Laboratory

	05 May 2005	11 May 2005	24 May 2005	02 Jun 2005	13 Jun 2005
ALAT	27	35	2477+	2142+	644+
ASAT	20	34	1544+	2700+	414+
gamma GT	50+	40	537+	813+	251+
LDH	474	681+	1498+	1860+	548+
Bilirubin	6.7	8.5	34.5+	247.9+	471.6+
AP	74	57	304+	341+	190+
Lipase	33	47	35	36	148+
Albumin	43	40	35	28+	27+

Normal range:
ALAT: 5-31 U/L
ASAT: 5-36 U/L
gamma GT: 5-46 U/L
LDH: 240-480 U/L
Bilirubin: 5.1-18.8 umol/L
AP: 35-104 U/L
Lipase: 0-60 U/L
Albumin: 34-48 g/L
+out of normal range

Local laboratory

	27 May 2005 10:33	27 May 2005 15:44	30 May 2005	01 Jun 2005	04 Jun 2005	08 Jun 2005	13 Jun 2005	16 Jun 2005	18 Jun 2005
ALAT	51.83 +	48.35 +	36.37 +	43.51 +	42.71 +	48.52 +	12.89 +	6.29+	4.21+
ASAT	37.12 +	31.9+	24.89 +	39.7+	60+	60+	7.22+	3.5+	2.42+
Bilirubin	136+	131+	166+	263+	339+	421+	473+	494+	458+
Bilirubin, conj.	98.4+								
Albumin		36.5			25.5+		26.2+	21.3+	22.1+
PT INR		1.8		1.4	1.9	3.4	3	3.2	
APTT		35.4			32.5	50.6+	55+	68+	

Normal range:
ALAT: 0.1-0.67 ukat/L
ASAT: 0.1-0.67 ukat/L
Bilirubin, total: 3-22 umol/L
Bilirubin, conj.< 5 umol/L
Albumin 35-52 g/L
+out of normal range

The investigator attributed the event to acute hepatitis B infection as not related to the study drug.

The autopsy was performed on (b) (6). The autopsy report under the liver section stated:

> "There are no inflammatory changes in the portobiliary spaces or in lobulae, which would indicate the presence of acute exacerbation of chronic hepatitis B (it is not possible to judge the presence of ground-glass cells due to autolysis). The autopsy report concluded "Postnecrotic fibrosis of the liver tissue with compensatory hyperplasia of the preserved parenchyma, corresponding to so call subacute necrosis (hepatodystrophy) – protracted liver damage without acute inflammatory changes (and parenchyma necroses). Toxic origin of the changes is probable. The cause of hemosiderosis of the liver tissue is not clear, might be associated with the treatment (transfusion?)".

The sponsor requested independent analysis by several external liver experts, including 2 pathologists who examined the histopathology. The followings are the conclusions from the 2 pathologists.

(b) (6)

In letter dated (b) (6), (b) (6) concluded:

> "My diagnosis is acute hepatitis B hepatitis with submassive hepatic necrosis, and possible partial regenerative failure. The H&E stained slide shows evidence of extensive recent hepatocellular loss (necrosis) with small regenerative hepatocellular nodules. Marked bile stasis and autolysis somewhat complicate histologic interpretation, but while the liver can now be described as cirrhotic there is relatively little actual fibrosis (confirmed by Masson stain). The changes are thus quite consistent with the 4 week duration of the reported clinical illness and there is nothing to suggest underlying liver disease of longer duration. The stain for Hepatitis B core antigen is positive in occasional hepatocyte nuclei while a stain for Hepatitis B surface antigen is negative. This is the expected pattern for acute Hepatitis B hepatitis and the absence of staining for surface antigen detracts from the possibility of acute hepatitis of another cause superimposed on symptomatic chronic Hepatitis B virus infection (as do the reported serum serologic studies and clinical history). The stain for Ki-67 (a cell proliferative marker) shows very little hepatocellular nuclear staining suggesting impaired regeneration as a factor in the rapid clinical progression to death in hepatic failure. Regenerative failure is uncommon in subjects with acute hepatitis, but when seen is generally in elderly subjects who often have chronic non-hepatic diseases (as was certainly true in this case)."

On (b) (6) (one of LAP members in Pathologic Subteam) concluded:

> "The main histopathological lesions in this post-mortem material consisted of submassive necrosis of the liver with slight fibrosis and suggestion of mild hepatocellular regenerative activity. Such lesions are consistent with the clinical course of the patient. As frequently observed in such cases of submassive necrosis, etiology cannot be formally determined, only on the basis of histological grounds. Taking into account the serological profile of hepatitis B viral markers in the present case, the lesions can be explained by severe hepatitis B viral infection, although histological findings were not specific and immunohistochemical results not conclusive. In fulminant viral B hepatitis, immunohistochemical expression of hepatocellular HBs and HBc antigens is expected to be absent at the time the liver is destroyed by viral infection. In the present case, it must be stressed that post-mortem autolysis precluded any formal conclusion concerning immunohistochemistry. Such lesions might also be consistent with drug-induced or toxic damage to the liver. However, there was no predominance of eosinophils in the inflammatory infiltration, and epithelioid and giant cell granulomas were not noted; these two latter lesions are frequently seen in drug-induced damage, especially when this damage is explained by an immunoallergic mechanism. The etiology of iron overload cannot be determined on histological grounds. It could be multifactorial: transfusions and/or necroinflammatory lesions and/or genetic abnormality?"

The Liver Advisory Panel evaluated this case. One member's assessment concluded that it was highly unlikely that the changes were drug related. He thought it was more likely that this was a case of hepatitis B exacerbated by immunosuppressive therapy in an elderly female with cancer. Another member's assessment also excluded the role of study drug.

Hepatic Disorder Adverse Events

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Treatment-emergent Adverse Events

The pooled incidence of treatment-emergent adverse events for hepatic disorders is presented in the following table. Overall, 86 subjects (9.7%) administered rivaroxaban had hepatic disorder events compared with 31 subjects (11.8%) administered heparin/VKA. The majority of hepatic disorder adverse events were laboratory abnormalities, which occurred in 69 subjects (7.8%) administered rivaroxaban and 31 subjects (11.8%) administered heparin/VKA. These laboratory adverse events most frequently included increases in ALT, AST, and GGT levels. It was noted that slightly more clinical events were reported in the rivaroxaban group as compared to heparin/VKA group in all categories except for liver-related investigations, signs and symptoms.

Incidence of Treatment-emergent Adverse Events for "Hepatic Disorders" in Phase 2 Treatment Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 11223 and 11528)

MSSO Search Category/ MedDRA Preferred Term	Total Rivaroxaban (N=883)		Heparin/VKA (N=263)	
Any event	**86**	**(9.7%)**	**31**	**(11.8%)**
MSSO: Cholestasis and jaundice of hepatic origin				
Any event	2	(0.2%)	0	(0.0%)
Cholestasis	1	(0.1%)	0	(0.0%)
Jaundice	1	(0.1%)	0	(0.0%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions				
Any event	11	(1.2%)	1	(0.4%)
Ascites ~	1	(0.1%)	0	(0.0%)
Hepatic failure	1	(0.1%)	0	(0.0%)
Hepatic lesion	1	(0.1%)	0	(0.0%)
Hepatic steatosis	4	(0.5%)	1	(0.4%)
Hepatotoxicity	1	(0.1%)	0	(0.0%)
Liver disorder	3	(0.3%)	0	(0.0%)
MSSO: Liver infections				
Any event	1	(0.1%)	0	(0.0%)
Hepatitis B	1	(0.1%)	0	(0.0%)
MSSO: Liver neoplasms, benign				
Any event	5	(0.6%)	1	(0.4%)
Hemangioma of the liver	3	(0.3%)	0	(0.0%)
Hepatic cyst	2	(0.2%)	1	(0.4%)
MSSO: Liver neoplasms, malignant and unspecified				
Any event	1	(0.1%)	0	(0.0%)
Hepatic neoplasm malignant recurrent	1	(0.1%)	0	(0.0%)
MSSO: Liver-related investigations, signs and symptoms				
Any event	69	(7.8%)	31	(11.8%)
ALT increased	39	(4.4%)	16	(6.1%)
Ascites ~	1	(0.1%)	0	(0.0%)
AST increased	27	(3.1%)	15	(5.7%)
Blood ALK PHOS increased	9	(1.0%)	2	(0.8%)
Blood bilirubin increased	3	(0.3%)	0	(0.0%)

GGT increased	33 (3.7%)	9 (3.4%)
Hepatic enzyme increased	5 (0.6%)	8 (3.0%)
Hepatic function abnormal	2 (0.2%)	1 (0.4%)
Hepatomegaly	0 (0.0%)	1 (0.4%)
Hypoalbuminemia	0 (0.0%)	1 (0.4%)
Liver function test abnormal	1 (0.1%)	0 (0.0%)
Transaminases increased	2 (0.2%)	2 (0.8%)

Key: ALK PHOS = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; MSSO = Maintenance Service and Support Organization; VKA = vitamin K antagonist
Note: All treatment-emergent events regardless of time after last study medication are included
Note: Incidence = # of events / # at risk, where:
# of events = # of subjects reporting the event reporting the event after start of treatment
at risk = # of subjects in reference population.
Note: Sorted alphabetically first by search category then by MedDRA preferred term.
Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories.

When analyzed separately by individual study, the incidence of any treatment-emergent hepatic disorder adverse event was lower on rivaroxaban (11.5%) compared with heparin/VKA (23.0%) in Study 11223. However, in study 11528, the incidence of any treatment-emergent hepatic disorder adverse event was much higher on rivaroxaban (7.7%) compared with heparin/VKA (1.5%) (See Table below).

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TREATMENT OF DEEP VEIN THROMBOSIS TABLE T/3.1.2 12MAR2008
BY-STUDY INCIDENCE OF TREATMENT EMERGENT ADVERSE EVENTS FOR MSSO MEDDRA SEARCH CATEGORY
'HEPATIC DISORDERS'
POPULATION: SUBJECTS VALID FOR SAFETY ANALYSIS
SN 11528

SEARCH CATEGORY MEDDRA PREFERRED TERM	BAY 59-7939 20 MG OD	BAY 59-7939 30 MG OD	BAY 59-7939 40 MG OD	BAY 59-7939 TOTAL	(LMW) HEPARIN / VKA
ANY BELOW MENTIONED SEARCH CATEGORY					
ANY EVENT	8 (5.93%)	10 (7.46%)	13 (9.56%)	31 (7.65%)	2 (1.46%)
MSSO: Cholestasis and jaundice of hepatic origin (SMQ)					
ANY EVENT	1 (0.74%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)
Jaundice	1 (0.74%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)
MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)					
ANY EVENT	0 (0.00%)	3 (2.24%)	3 (2.21%)	6 (1.48%)	0 (0.00%)
Ascites ~	0 (0.00%)	0 (0.00%)	1 (0.74%)	1 (0.25%)	0 (0.00%)
Hepatic failure	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (0.25%)	0 (0.00%)
Hepatic steatosis	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (0.25%)	0 (0.00%)
Hepatotoxicity	0 (0.00%)	1 (0.75%)	0 (0.00%)	1 (0.25%)	0 (0.00%)
Liver disorder	0 (0.00%)	0 (0.00%)	2 (1.47%)	2 (0.49%)	0 (0.00%)
MSSO: Liver neoplasms, benign (SMQ)					
ANY EVENT	1 (0.74%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)
Haemangioma of liver	1 (0.74%)	0 (0.00%)	0 (0.00%)	1 (0.25%)	0 (0.00%)
MSSO: Liver neoplasms, malignant and unspecified (SMQ)					
ANY EVENT	0 (0.00%)	0 (0.00%)	1 (0.74%)	1 (0.25%)	0 (0.00%)
Hepatic neoplasm malignant recurrent	0 (0.00%)	0 (0.00%)	1 (0.74%)	1 (0.25%)	0 (0.00%)
MSSO: Liver related investigations, signs and symptoms (SMQ)					
ANY EVENT	6 (4.44%)	7 (5.22%)	11 (8.09%)	24 (5.93%)	2 (1.46%)
Alanine aminotransferase increased	4 (2.96%)	2 (1.49%)	1 (0.74%)	7 (1.73%)	0 (0.00%)
Ascites ~	0 (0.00%)	0 (0.00%)	1 (0.74%)	1 (0.25%)	0 (0.00%)
Aspartate aminotransferase increased	1 (0.74%)	1 (0.75%)	1 (0.74%)	3 (0.74%)	1 (0.73%)
Blood alkaline phosphatase increased	1 (0.74%)	0 (0.00%)	2 (1.47%)	3 (0.74%)	0 (0.00%)
Gamma-glutamyltransferase increased	5 (3.70%)	5 (3.73%)	5 (3.68%)	15 (3.70%)	1 (0.73%)
Hepatic enzyme increased	0 (0.00%)	0 (0.00%)	2 (1.47%)	2 (0.49%)	0 (0.00%)
Hepatic function abnormal	0 (0.00%)	0 (0.00%)	2 (1.47%)	2 (0.49%)	0 (0.00%)

Deaths

There was one liver-related death (Subject 11223-506006) that occurred in Study 11223 in the Phase 2 DVT treatment studies. This case was discussed in the previous section.

Serious Adverse Events

The incidence of hepatic disorder serious adverse events was similar between the 2 treatment groups (see Table below). Overall, 7 subjects (0.8%) administered rivaroxaban and 4 subjects (1.5%) administered the comparator reported serious adverse events. The majority of serious adverse events were laboratory abnormalities, which occurred in 4 subjects (0.5%) receiving rivaroxaban compared with 4 subjects (1.5%) receiving the comparator.

In Study 11223, there were 4 (0.8%, 1 hepatitis B and LFT abnormalities) and 4 (3.2%, all LFT abnormalities) subjects reporting a hepatic disorder serious adverse event on rivaroxaban and heparin/VKA respectively.

In Study 11528, there were 3 (0.7%, 4 events: jaundice, ascites, hepatic failure, hepatic neoplasm malignant recurrent) and 0 (0%) subjects reporting a hepatic disorder serious adverse event on rivaroxaban and heparin/VKA respectively.

Incidence of Serious Treatment-Emergent Adverse Events from MSSO Search Categories of Hepatic Disorders in Phase 2 Treatment Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 11223 and 11258)

MSSO Search Category/ MedDRA Preferred Term	Total Rivaroxaban (N=883)	Heparin/VKA (N=263)
Any event	**7 (0.8%)**	**4 (1.5%)**
MSSO: Cholestasis and jaundice of hepatic origin		
Any event	1 (0.1%)	0 (0.0%)
Jaundice	1 (0.1%)	0 (0.0%)

MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions		
Any event	2 (0.2%)	0 (0.0%)
Ascites ~	1 (0.1%)	0 (0.0%)
Hepatic failure	1 (0.1%)	0 (0.0%)
MSSO: Liver infections		
Any event	1 (0.1%)	0 (0.0%)
Hepatitis B	1 (0.1%)	0 (0.0%)
MSSO: Liver neoplasms, malignant and unspecified		
Any event	1 (0.1%)	0 (0.0%)
Hepatic neoplasm malignant recurrent	1 (0.1%)	0 (0.0%)
MSSO: Liver-related investigations, signs and symptoms		
Any event	4 (0.5%)	4 (1.5%)
ALT increased	1 (0.1%)	3 (1.1%)
Ascites ~	1 (0.1%)	0 (0.0%)
AST increased	2 (0.2%)	2 (0.8%)
Blood ALK PHOS increased	1 (0.1%)	0 (0.0%)
GGT increased	2 (0.2%)	0 (0.0%)
Hepatic enzyme increased	0 (0.0%)	1 (0.4%)
Liver function test abnormal	1 (0.1%)	0 (0.0%)

Key: ALK PHOS = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; MSSO = Maintenance Service and Support Organization; VKA = vitamin K antagonist
Note: All treatment-emergent events regardless of time after last study medication are included
Note: Incidence = # of events / # at risk, where:
# of events = # of subjects reporting the event reporting the event after start of treatment
at risk = # of subjects in reference population
Note: Sorted alphabetically first by search category then by MedDRA preferred term.
Note: MedDRA preferred terms marked with ~ are allocated to multiple search categories.

Adverse Events Leading to Study Discontinuation

In Phase 2 treatment studies in VTE, 3 subjects (0.3%) administered rivaroxaban discontinued from the study due to liver-related adverse events, including 2 subjects with increased laboratory values and 1 subject with hepatitis B. No subjects treated with heparin/VKA discontinued early due to adverse events.

7.3.4.4.2.3 Atrial Fibrillation Studies (Studies 11390, 11866, and 12024)

Three Phase 2 studies in subjects with atrial fibrillation were conducted in Japan. One of the Phase 2 studies was uncontrolled (Study 11390), and the other 2 studies used warfarin as the active control. Each of the studies was approximately 1 month in duration. Subjects with transaminases ≥2x ULN were excluded from enrollment in these studies.

Clinical Laboratory Measurements

In the Phase 2 studies in subjects with atrial fibrillation, liver-related laboratory assessments were performed at the intervals indicated in the following table.

Schedule of Liver-related Laboratory Assessments in Phase 2 Studies in Atrial Fibrillation

(Studies 11390, 11866, and 12024)

Study	Screen	Day 1	Day 14	Day 28	Follow-up[a]
11390	X	X		X	X
11866	X	X	X	X	X
12024	X	X		X	X

[a] 28 (±7) days after the last dose of study medication

Liver-related Laboratory Values

Treatment-emergent laboratory abnormalities are presented individually for the 3 studies in atrial fibrillation below. A laboratory abnormality was defined in the protocol as a value that exceeded the upper limit of normal range. Additional analyses at higher thresholds (i.e., 3x ULN) were not done.

In Study 11866, subjects administered rivaroxaban had a higher incidence of ALT and AST levels above the upper limit of normal compared with subjects administered warfarin (see table below). The highest incidence of treatment-emergent high laboratory abnormalities for ALT was observed in the rivaroxaban 10 mg group (19.0%) as compared to warfarin (4%). Two subjects receiving rivaroxaban experienced both increases of AST > 2 x ULN and ALT > 2 x ULN; 1 subject (Subject 200060005) in the 15 mg od group had the peak levels of AST (307 U/L, > 7 x ULN) and ALT (557 U/L, > 12 x ULN) at Visit 2 (Day 14), and 1 subject (Subject 200060004) in the 20 mg od group had the peak levels of AST (146 U/L, > 3 x ULN) and ALT (328 U/L, > 7 xULN) at Visit 3 (Day 28). The AST and ALT levels returned to the normal range within 21 days after the last dose of the study medication. Their total and direct bilirubin levels were normal during the study period.

Table 2-19: Incidence of Treatment-emergent Increased Laboratory Abnormalities (>1x ULN) (Subjects Valid for Safety Analyses in Study 11866)

Laboratory Test	RIVA 10 mg od (N=26)	RIVA 15 mg od (N=25)	RIVA 20 mg od (N=24)	Warfarin od (N=27)
Alanine aminotransferase	4/21 (19.0%)	3/19 (15.8%)	3/22 (13.6%)	1/25 (4.0%)
Aspartate aminotransferase	3/23 (13.0%)	2/18 (11.1%)	1/21 (4.8%)	2/23 (8.7%)
Total bilirubin	2/23 (8.7%)	3/22 (13.6%)	2/22 (9.1%)	4/25 (16.0%)
Gamma-glutamyltransferase	1/16 (6.3%)	1/11 (9.1%)	0/15 (0.0%)	2/19 (10.5%)
Alkaline phosphatase	1/23 (4.3%)	0/23 (0.0%)	0/23 (0.0%)	1/25 (4.0%)

Key: od = once daily; RIVA = rivaroxaban
Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the abnormality after start of treatment to 7 days after the last dose of study drug, and
at risk = # of subjects with readings before and after the start of treatment who did not report the abnormality before treatment
Note: When more than 1 measurement was available for a subject at baseline, the last value was used for analysis.
Note: When more than 1 measurement was available for a subject postbaseline, the maximum value was used for analysis.

In Study 12024, there were few events of any laboratory abnormality >1x ULN (see Table below). One subject (4.3%) administered rivaroxaban 10 mg bid had an ALT value above the upper limit of normal compared with 2 subjects (8.3%) administered warfarin.

**Incidence of Treatment-emergent Increased Laboratory Abnormalities (>1x ULN)
(Subjects Valid for Safety Analyses in Study 12024)**

Laboratory Test	RIVA 2.5 mg bid (N=24)	RIVA 5 mg bid (N=26)	RIVA 10 mg bid (N=24)	Warfarin od (N=26)
Alanine aminotransferase	0/21 (0.0%)	0/25 (0.0%)	1/23 (4.3%)	2/24 (8.3%)
Aspartate aminotransferase	0/18 (0.0%)	1/25 (4.0%)	1/21 (4.8%)	0/24 (0.0%)
Total bilirubin	0/20 (0.0%)	2/26 (7.7%)	0/23 (0.0%)	0/24 (0.0%)
Gamma-glutamyltransferase	1/10 (10.0%)	1/24 (4.2%)	0/15 (0.0%)	0/13 (0.0%)
Alkaline phosphatase	2/18 (11.1%)	0/25 (0.0%)	0/23 (0.0%)	0/24 (0.0%)

Key: bid = twice daily; od = once daily; RIVA = rivaroxaban
Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the abnormality after start of treatment to 7 days after the last dose of study drug, and
at risk = # of subjects with readings before and after the start of treatment who did not report the abnormality before treatment
Note: When more than 1 measurement was available for a subject at baseline, the last value was used for analysis. When more than 1 measurement was available for a subject postbaseline, the maximum value was used for analysis.

ALT or AST >3x ULN With a Concurrent Total Bilirubin >2x ULN

In Studies 11390, 11866, and 12024, there were no subjects with ALT or AST levels >3xULN concurrent with a total bilirubin level >2x ULN.

Hepatic Disorder Adverse Events

Treatment-emergent Adverse Events

In Study 11390, INR increased in 3 subjects who received rivaroxaban 20 mg bid and GGT increased in 1 subject who received rivaroxaban 10mg bid (see table below).

**Incidence of Treatment-emergent Hepatic Disorder Adverse Events
(Subjects Valid for Safety Analyses in Study 11390)**

System Organ Class MedDRA Preferred Term	RIVA 10 mg bid (N=25)	RIVA 20 mg bid (N=11)	Total (N=36)
Investigations			
International normalized ratio increased	0 (0%)	3 (27%)	3 (8%)
GGT increased	1 (4%)	0 (0%)	1 (3%)

Key: bid = twice daily; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; RIVA = rivaroxaban
Note: Includes only treatment-emergent events that occurred up to 7 days after the last dose of study medication.
Note: Incidence = # of events / # as risk, where:
# of events = # of subjects reporting the abnormality after the start of treatment
at risk = # of subjects with readings before and after start of treatment who did not report the abnormality before treatment

In Study 11866, few events were reported and all events were LFT abnormalities.

Incidence of Treatment-emergent Hepatic Disorder Adverse Events (Subjects Valid for Safety Analyses in Study 11866)

System Organ Class MedDRA Preferred Term	RIVA 10 mg od (N=26)	RIVA 15 mg od (N=25)	RIVA 20 mg od (N=24)	Warfarin od (N=27)
Hepatobiliary disorders				
Hepatic function abnormal	0 (0.0%)	1 (4.0%)	1 (4.2%)	0 (0.0%)
Investigations				
ALT increased	2 (7.7%)	0 (0.0%)	1 (4.2%)	2 (7.4%)
AST increased	1 (3.8%)	0 (0.0%)	0 (0.0%)	2 (7.4%)
Blood bilirubin increased	0 (0.0%)	1 (4%)	0 (0.0%)	0 (0.0%)
GGT increased	0 (0.0%)	1 (4%)	0 (0.0%)	0 (0.0%)

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; od = once daily; RIVA = rivaroxaban
Note: Includes only treatment-emergent events that occurred up to 7 days after the last dose of study medication.
Note: Incidence = # of events / # as risk, where:
# of events = # of subjects reporting the abnormality after the start of treatment
at risk = # of subjects with readings before and after start of treatment who did not report the abnormality before treatment

In Study 12024 (see table below), hepatic cirrhosis was reported in 1 subject in the rivaroxaban group and 1 alcoholic liver disease was reported in the warfarin group.

Incidence of Treatment-emergent Hepatic Disorder Adverse Events (Subjects Valid for Safety Analyses in Study 12024)

System Organ Class MedDRA Preferred Term	RIVA 2.5 mg bid (N=24)	RIVA 5 mg bid (N=26)	RIVA 10 mg bid (N=24)	Warfarin od (N=26)
Hepatobiliary disorders				
Hepatic cirrhosis	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Alcoholic liver disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
Investigations				
Blood bilirubin increased	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GGT increased	0 (0.0%)	1 (3.8%)	1 (4.2%)	0 (0.0%)

Key: bid = twice daily; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; od = once daily; RIVA = rivaroxaban
Note: Includes only treatment-emergent events that occurred up to 7 days after the last dose of study medication.
Note: Incidence = # of events / # as risk, where:
# of events = # of subjects reporting the abnormality after the start of treatment
at risk = # of subjects with readings before and after start of treatment who did not report the abnormality before treatment

Hepatic cirrhosis was reported in a 78-year-old woman (12024-200050002) who had medical history of chronic hepatitis (1995), hepatitis B carrier (1995), and hepatic cirrhosis (2005). Rivaroxaban 2.5 mg BID began on 13 Oct 2005 and continued for 8 days. On (b) (6) , the patient visited the hospital for having left abdominal pain. Ascites retention was confirmed by ultrasonograph. The study drug was withdrawn. On (b) (6) she was hospitalized and was diagnosed with aggravation of hepatic cirrhosis (ascites retention), considered serious due to important medical event. ALT was normal. She was treated and was transferred to another hospital on (b) (6) No additional information was available because the subject refused to provide further information. The investigator considered the event as not related to the study drug.

Deaths

No deaths and liver-related deaths were reported in the 3 Phase 2 studies in subjects with atrial fibrillation.

Serious Adverse Events

Two subjects receiving rivaroxaban had hepatic disorder serious adverse events: one had abnormal hepatic function and another one had hepatic cirrhosis (discussed above). No serious adverse events were reported in the warfarin group.

Abnormal hepatic function was reported in a 70-year-old woman who had a medical history of hypertension, chronic heart failure, hypertrophic cardiomyopathy and angina pectoris. The subject received BAY 59-7939 15 mg od from 26 Aug 2006 to 15 Sep 2006. On (b) (6)), she presented with ALT 557 U/L (> 10xULN), AST 307 U/L, LDH 388 U/L, GGT 50 U/L, but no elevation of bilirubin (T-Bil 0.8 mg/dL). On (b) (6), ALT decreased to 311 U/L and rivaroxaban was discontinued permanently due to this event. Abdominal ultrasound investigation and CT were performed but showed no abnormality. Echocardiography, ECG or Chest X-rays showed no significant change, compared to the investigations performed prior to initiating the study medication. On (b) (6) ALT and AST returned to the normal ranges. The investigator assessed the event as study drug-related.

Adverse Events Leading to Study Discontinuation

The same two subjects discussed under Serious Adverse Events above had serious hepatic disorder adverse events that led to study discontinuation.

7.3.4.4.3 Ongoing Studies

ALT >3x ULN Concurrent With TB>2x ULN

There were total of 27 subjects who had ALT >3 xULN concurrent with total bilirubin >2xULN identified in ongoing studies based on 6-month safety update based on cutoff date of 31 October 2008 for J-ROCKET-AF; cutoff date of 5 December 2008 for other studies. Only ATLAS ACS TIMI 46 and EINSTEIN DVT/PE studies were open-label studies and other studies are blinded studies.

In ATLAS ACS TIMI 46 study, 3 cases with ALT> 3xULN concurrent with TB>2xULN were reported in the placebo group (see Table below). Among the 3 cases, 1 subject had sepsis with hypotension, multi-organ failure and subsequently died; 2 subjects had pancretitis with elevated LFTs.

ATLAS ACS TIMI 46: ALT >3x ULN Concurrent With TB>2x ULN Cases (All in Placebo group)

Age/ sex	Exposed Days	**Event Days**	**ALT (U/L)/ TB (mg/dL)**	**Outcomes**	**LAP Assessment**
44/F	91	(b) (6)	ALT 134/ TB 11	Sepsis on Day 91.Bradycardia, hypotension, worsening liver failure and multi-organ failure on Day 108. Subject died from multi-organ failure including liver failure and lower respiratory tract infection on Day (b) (6)	Not related
57/M	32	(b) (6)	ALT 561/ TB 3.3	Acute pancreatitis on Day 32	-
66/M	19	(b) (6)	ALT 596/ TB 3.5	Pancreatitis on Day 125.	-

In EINSTEIN DVT/PE study, 3 cases with ALT> 3xULN concurrent with TB>2xULN were reported in the rivaroxaban group (see Table below). One subject had dilated cardiomyopathy and later was transferred to another hospital for terminal care. One subject had cancers and subsequently died. The remaining one subject had acute severe hepatitis with liver failure and subsequently died. The patient narratives and available Liver Advisory Panel assessment are included following these tables.

EINSTEIN DVT/PE: ALT >3x ULN Concurrent With TB>2x ULN Cases (All in Rivaroxaban Group)

Age/ sex	Exposed Days	**Event Days**	**ALT (U/L)/ TB (mg/dL)**	**Outcomes**	**LAP Assessment**
77/F White 400011004	169	(b) (6)	ALT 698/ TB 4.1	Hospitalized for dilated cardiomyopathy on Day 166. Discharged from hospital on 183 to another hospital for terminal care. None of these events had resolved as of (b) (6).	-
63/F 11702-16018-1005	18	(b) (6)	ALT 5371/ TB 67 mcmol/L	Hospitalized for dyspnea and asthenia on Day 16. Severe acute hepatitis and liver insufficiency was diagnosed on Day 18. Patient died on Day 26.	Likely drug-induced toxic injury by one member.
71/M White 220131004	35	(b) (6)	ALT 513/ TB 5.4	Gastric cancer with liver metastasis was found. Subject died on Day 56. No autopsy was performed.	-

Sixteen subjects with ALT>3xULN concurrent with TB>2xULN were reported from ROCKET-AF study including 6 cases submitted in 6-month safety update. Three were reported in the J-

ROCKET-AF study. Both studies are blinded studies. Two cases in ROCKET-AF were unblinded and both had received warfarin. Three subjects in ROCKET-AF study subsequently died and remained unblended. One case in J-ROCKET-AF study was unblinded and had received rivaroxaban.

ROCKET-AF: ALT >3x ULN Concurrent With TB>2x ULN Cases (Blinded)

Age/ sex	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment
58/M White 100338	46	(b) (6)	ALT 647/ TB 3.6	Acute hepatitis C was diagnosed.	Not related
78/M White 100650	200	(b) (6)	ALT 156/ TB 3.8	Metastatic pancreatic carcinoma to liver was diagnosed. Died on Day 331.	-
71/M White 100966	45	(b) (6)	ALT 1797/ TB 6.1	Hospitalized for worsening heart failure on Day 33. Resolved on Day 83.	-
48/M Asian 101271	96	(b) (6)	ALT 443/ TB 13.1	Hospitalized for CHF on Day 93. Resolved on Day 127.	Not related
62/F American Indian/Alaskan native 101773	32	(b) (6)	ALT 1457/ TB 12.1	Acute hepatitis B was diagnosed. ALT was normal on Day 107. Subject received warfarin.	-
87/F Asian 104083	104	(b) (6)	ALT 104/ TB 2.5	Resolved 1 week later on study drug.	-
84/M White 100044	462	(b) (6)	ALT 167/ TB 2.4	Cardiac failure congestive on Day 454. Subject received warfarin.	-
73/M White 103861	178	(b) (6)	ALT 222/ TB 2.5	Resolved on Day 211.	-
79/M White 105428	168	(b) (6)	ALT 218/ TB 4.9	Gallstone/obstructive hepatitis was diagnosed.	-

72/M Asian 109730	22	(b) (6)	ALT 553/ TB 2.8	Cardiac failure congestive on Day 23. Resolved on Day 40.	-

Table 19: Individual Subjects With ALT >3x ULN and Total Bilirubin >2x ULN (Subjects Available for Safety in ROCKET-AF)(Continued)

Subject ID Age/Sex	TTD (days)	Peak Laboratory Values[b]	Corresponding Peak Laboratory Ratios[a]	Comments
104111 Figure 2 in Study 11630 76/female	359	ALT = 250 U/L (Day 307) AST = 295 U/L (Day 307) TB = 6.61 mg/dL (Day 307) DB = 2.98 mg/dL (Day 307) AP = 384 U/L (Day 307)	7.81 8.68 5.38 7.29 2.84	Cholangitis (inflammatory disease because of obstruction in biliary ducts) reported on Day 307.
105059 Figure 2 in Study 11630	225	ALT = 147 U/L (Day 224) AST = 133 U/L (Day 224) TB = 5.80 mg/dL (Day 224) DB = 1.20 mg/dL (Day 224) AP = 148 U/L (Day 224)	12.25 11.08 4.83 6.00 0.78	Upper GI bleed Day 223 and cardiogenic shock Day 225. Subject died on Day 225.
103820 Figure 2 in Study 11630 80/male	351	ALT = 177 U/L (Day 353) AST = 260 U/L (Day 353) TB = 8.10 mg/dL (Day 353) DB = 3.60 mg/dL (Day 353) AP = 153 U/L (Day 353)	3.54 6.19 6.75 9.00 1.28	Cholecystitis on Day 42 and bile duct obstruction on Day 352.
106725 Figure 2 in Study 11630 58/female	222	ALT = 366 U/L (Day 219) AST = 102 U/L (Day 219) TB = 2.63 mg/dL (Day 219) DB = 1.35 mg/dL (Day 219) AP = 137 U/L (Day 219)	10.76 3.00 2.14 3.29 1.11	Abnormal liver function test reported on Day 219. Abdominal ultrasound showed liver enlargement and fat hepatosis. Additional information being sought.
109103 Figure 2 in Study 11630 60/female	82	ALT = 371 U/L (Day 77) AST = 332 U/L (Day 77) TB = 4.78 mg/dL (Day 77) and 5.63 mg/dL (Day 78) DB = 3.56 mg/dL (Day 77) and 4.42 mg/dL (Day 78) AP = 199 U/L (Day 77)	6.75 8.97 3.98 4.69 11.87 14.73 1.46	Cholecystitis and pancreatitis reported on Day 76. Treatment code broken by investigator; subject received warfarin.
110588 Figure 2 in Study 11630 66/female	85	ALT = 701 U/L (Day 62) AST = 2185 U/L (Day 62) TB = 3.53 mg/dL (Day 62) AP = 407 U/L (Day 62)	10.78 59.05 3.53 2.99	Cardiogenic shock on Day 60.

J-ROCKET-AF: ALT >3x ULN Concurrent With TB>2x ULN Cases (Blinded)

Age/ sex	Exposed Days	Event Days	ALT (U/L)/ TB (mg/dL)	Outcomes	LAP Assessment
81/M Asian 200600003	121	(b) (6)	ALT 445/ TB 3.6	Gallbladder stone detected on Day 125. Resolved on Day 146.	-

65/M Asian 200940010	77	(b) (6)	ALT 388/ TB 3.7	Abdominal pain on Day 76. Resolved on Day 106.	-
66/M Asian 201310004	12	(b) (6)	ALT 340/ TB 9.3	Nausea started Day 7. Perihepatic ascites by CT on Day 22. Diagnosed of suspected drug-induced liver disorder on day 22. Resolved Day 94. Treatment code broken by investigator; subject received rivaroxaban.	-

Two additional cases were reported in MAGELLaN study in medically ill patients. One subject subsequently died and had received enoxaparin after unblinding.

Table 31: Individual Subjects With ALT >3x ULN and Total Bilirubin >2x ULN (Subjects Valid for Safety in MAGELLaN)

Subject ID Age/Sex	Total Treatment Duration (days)	Peak Laboratory Values[b]	Corresponding Peak Laboratory Ratios[a]	Possible Alternative Etiologies for Lab Findings
280130001 Figure 2 in Study 12839 72/female	28	ALT = 520 U/L (Day 28); 429 U/L (Day 29) AST = 405 U/L (Day 27) and 252 U/L (Day 28) TB = 2.2 mg/dL (Day 28); 3.0 mg/dL (Day 29) DB = 1.6 mg/dL (Day 28); 2.3 mg/dL (Day 29) AP = 29 U/L (Day 29)	12.68 10.46 10.95 6.81 1.83 2.47 5.40 7.50 0.21	Cardiac and renal insufficiency, fatal multiple organ failure. Subject died on Day 29. Treatment code broken; subject received enoxaparin.
440070002 Figure 2 in Study 12839 67/male	2	ALT = 8078 U/L (Day 3); 478 U/L (Day 9) AST = 17384 U/L (Day 3); 86 U/L (Day 9) TB = 7.0 mg/dL (Day 9) DB = 7.8 mg/dL (Day 3); 3.9 mg/dL (Day 9)	179.51 11.12 496.69 2.32 5.48 26.10 12.09	History of heart failure and elevated AST, ALT and TB levels starting 7 months prior to the first dose of study drug. At baseline, subject had pneumonia with Troponin T and pro-BNP levels increased consistent with acute coronary syndrome and CHF.

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = direct bilirubin; TB = total bilirubin; AP = alkaline phosphatase

[a] Ratio = lab value divided by the corresponding Upper Limit of Normal (ULN). Ratio provided when ULN available.

[b] More than 1 laboratory value could be provided when peak elevations for analytes occur on different days.

For subject 11702-16018-1005 who developed severe acute hepatitis and liver insufficiency and subsequently died in EINSTEIN DVT/PE study, the following is the patient's narrative.

11702-16018-1005

This is a 63 year-old female originally from Madagascar and moving to France in 1995. She had a medical history of hypertension (since 1994), severe asthma on oral cortisteroids for 10 years, severe asthma exacerbation requiring intubation (1997), pulmonary emphysema, recent asthma exacerbation (11/2007). The subject had echocardiography in December 2006 which showed normal left and right chambers, normal cardiac valves, left ventricular relaxation dysfunction, and a non-significant pericardial effusion of 5 mm. She had a 34 pack year history of cigarette use, discontinued one year previously. She had no past history of liver disease or alcohol abuse (EtOH occasional) but did have an increased GGT. Corticosteroid-induced diabetes had been recently diagnosed.

The subject received rivaroxaban 15 mg bid from 28 Dec 2007 to 14 Jan 2008 for acute multi-segmental PE in right lower lobe detected by CT scan on 27 Dec 2007. The patient received heparin on 27 Dec 2007 prior to enrollment. On enrollment on 28 Dec 2007, lab showed ALT 49, TB 12 micromol/L, and GGT 441. The patient showed clinical improvement and had been discharged on 07 Jan 2008 (Day 11).

In the time between 07 Jan and 12 Jan 2008 the patient had episodes of disorientation at home and increase of dyspnea according the patient's daughter. Deroxat (paroxetine) had been started on 05 Jan 2008 because of reactional depression.

On (b) (6) the patient had been re-admitted due to increase of dyspnea and deep asthenia. Upon admission, the patient showed tachycardia and new respiratory exacerbation without clinical signs of right heart failure. The blood pressure in admission was 120/80 mmHg and O2 Sat was 96% at room air. Neither episode of acute hypotension nor signs of cardiac decompensation were described. She was treated for asthma exacerbation and improved with a decrease of the wheezing. No liver function tests were done.

On Jan. 14, 2008 (b) (6) lab showed ALT 5371 UL, AST 10506 U/L, TB 67 micromol/L, AP 151 U/L, GGT 538 U/L, PT < 10%, FV <10%, D-dimer >4000, platelet 121,000 (decreased from 301,000 on 12 Jan 2008), B-type natriuretic peptide (BNP; norm < 100pg/ml): 1610, and Creatinine 180 μmol/L (increased from 113 μmol/L on 12 Jan 2008). Severe acute hepatitis and liver insufficiency was diagnosed. Rivaroxaban was stopped.

On (b) (6) she was transferred to surgical ICU of another hospital with the diagnosis of acute liver failure potentially related to study drug and consideration for liver transplant. The BP was 109/68 mmHg during the transfer. Abdominal ultrasound reported "The ultrasonographic appearance was in support of hepatitis with a layered appearance of the gall bladder wall on the hepatic side. Discovery of a tumor mass 6 cm diameter at the upper pole of the right kidney." Thoracoabdominal CT showed right segmental pulmonary embolism (suspect of left lingular subsegmental thrombosis) and 6 cm tumor mass in right kidney, highly suspicious of malignancy. Hepatitis serology test showed previous hepatitis B (positive HBcAb and negative HBsAg) and negative for hepatitis C. Transthoracic Echocardiogarphy (TTE) showed LA surface area = 40 cm^2, E/A >1, PAPS = 50-55 mmHg, LVEF 40%, sub-aortic gradient 7 cm at maximum, RV/RA dilatation, chambers free of any visible thrombi; no pericardial effusion. Upon arrival, the patient had a BP of 100/70, HR of 107 bpm, a regular sinus rhythm, conjunctical icterus, hepato-jugular reflux and hematomas and petechia at the puncture site. The patient was apyretic and no hepatomegaly was observed. Lung radiographic and laboratory findings showed no abnormalities except for a high white blood cell count and moderate renal insufficiency.

On 17 Jan 2008 (b) (6) TTE showed hypokinetic left ventricle with a heart-rate dependent flow.

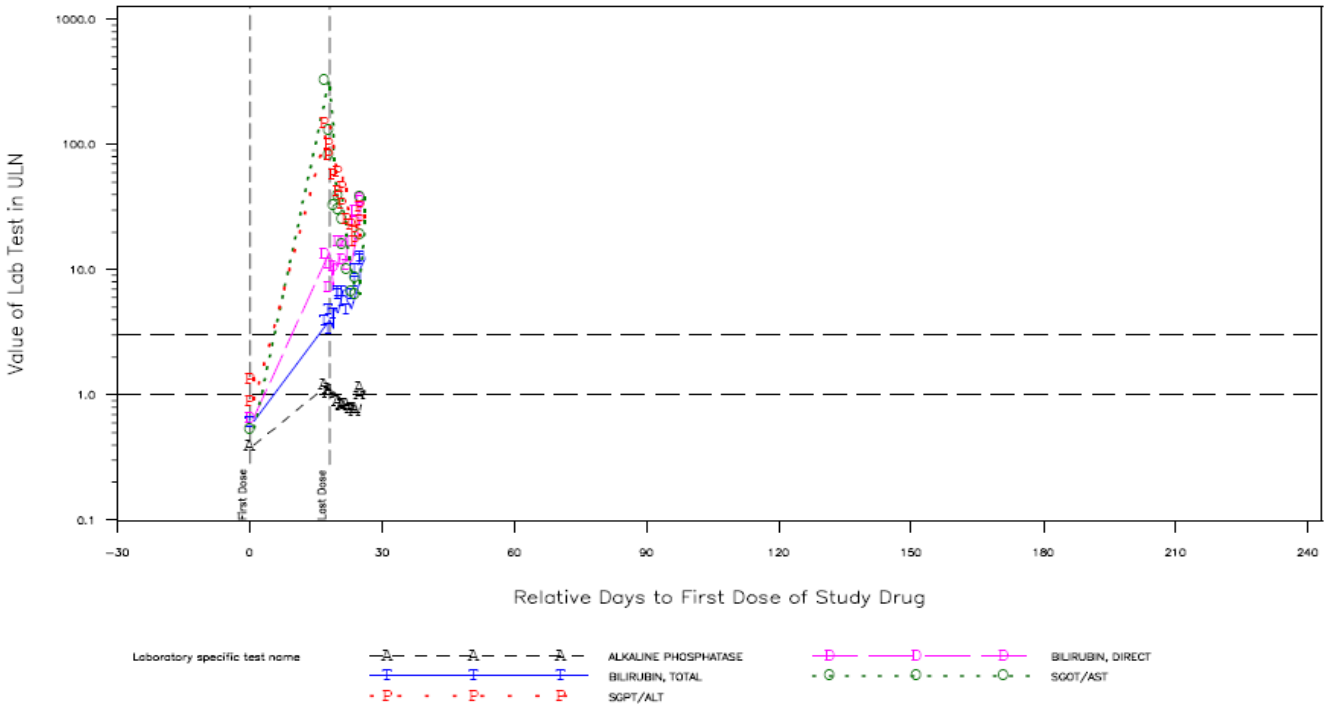
On 19 Jan 2008 (b) (6) resumption of anti-coagulant therapy with unfractionated heparin 12000 U/24h, in a context of pulmonary embolism, with probable thrombogenic renal cancer.
On 20 Jan 2008 (b) (6) TTE (pt on dobutamine) showed LV fraction of 34%, E/A >1 and obstructed PAP of 11; systolic PAP of 36 mmHg, VTI =5.4 and an estimated cardiac output of 2.2 L/min. Lack of any increased troponin levels and lack of significant changes in ECG were noted by physician.

On (b) (6) the patient experienced another episode of myocardial failure with agitation and hypotension; and at the end of TTE, the patient suffered from cardiac arrest through asystole which was treated immediately with recovery of precarious hemodynamic condition at 15 minutes of resuscitation and followed by multiple organ failure. TTE showed dilated cardiopathy with increased pressures (i.e. LVEF = 30%)

On (b) (6), the patient died with multi-organ failure.

Autopsy was performed on (b) (6) concluded "Principle observations: hematoma on the anterior aspect of the kidney opposite the tumor process. Cardiac liver. Probable thrombosis of the ilio-femoral veins, the vena cava was patent." Under liver, it stated "Congested liver with dilation of sinusoid cavities". Additional heart and lung report showed "Heart: massive dilation of the right ventricle and left ventricular hypertrophy, adipose involution of the right ventricular wall, and partially of the left ventricle, compatible with arrhythmia-inducing right ventricular dysplasia (ARVD); Coronary arteries: lesions of atheroma and 40% stenosis of the left coronary artery and the anterior IV artery, without occlusion, without recent thrombosis, absence of a recent or old ischemic area; Lungs: recent thrombus of a segmental artery of the right lower lobe grafted onto an organized old thrombus, sequelae of chronic bronchial inflammation". Microscopy examination stated "The hepatic parenchyma was the seat of a hemorrhagic necrosis in the central lobe area and a macrovacuolar steatosis. There was no argument in favor of a drug-related hepatitis. The kidney had partly undergone autolysis. We observed a few obsolete glomeruli. Moreover, there was a slight lymphocytic inflammatory infiltrate, evoking chronic interstitial nephropathy. We observed an old organizing hematoma in the perirenal fat with presence of a very large number of foamy macrophages. There was no tumor cell proliferation."

The following figure shows the liver-related laboratory values over time.



The following are assessments made by members of Liver Advisory Panel:

Professor Y. Horsmans, Clinical, Germany (b) (4)

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In conclusion, rivaroxaban causality is **unlikely**. The most probable cause is ischemic hepatitis mainly based on the clinical and biological evolution observed after January 14th. Moreover, the cause of death is clearly related to cardiac failure. However, it is impossible to definitively exclude rivaroxaban causality in the liver function tests perturbation observed on (b) (6) since no episode of cardiac failure, hypotension was described at that time.

(b) (6)

The histopathological findings in the liver as well as in the kidney are highly suggestive of circulatory failure.

Indeed, hemorrhagic necrosis in the centrilobular areas of the liver, minimal thickening of the terminal hepatic veins and mild centrilobular perisinusoïdal fibrosis, with minimal inflammatory infiltration, absence of lesions of the hepatocytes in the periportal areas and absence of portal or periportal fibrosis, are consistent with acute cardiac failure, possibly surimposed to mild liver injury secondary to chronic cardiac failure.

The lesions observed in the renal parenchyma are also consistent with such an hypothesis.

There is no positive histopathological argument favoring hepatotoxicity on the present liver sample obtained at necropsy. Although the centrilobular predominance of hepatocellular necrosis is suggestive of drug induced injury, hemorrhage is rare, and there usually are other lesions such as the presence of apoptotic hepatocytes and more pronounced portal and lobular inflammatory infiltration than was observed in the present case. Also, eosinophils and epithelioid and giant cell granulomas are expected, particularly if the hepatotoxicity is to be explained by an immunoallergic mechanism.

Dr. Daminique Larrey, M.D., Ph.D., Clinical, France

Statement dated (b) (4)

CONCLUSION :

Case of acute liver failure followed by death. Death was largely related to severe cardiac dysfunction.

The role of the study drug appears very unlikely on the clinical presentation and the very important findings made at autopsy and subsequent histological liver examination which strongly argue for a liver ischemia caused by cardiac dysfunction.

D Larrey comments (b) (4)

The initial episode of acute hepatitis occurs on (b) (6) The major increase in serum transaminases with a ratio AST/ALT >> 1 associated with very high LDH and CK ,followed by a very rapid drop of these enzymes are in favour of a tissue ischemia in line with acute renal failure. The absence of hypotensive episode and cardiac distress between (b) (6) does not allow proving an ischemic event, definitely. However, there are evidences in the literature showing that such events may be missed (extensively reviewed in Valla D, Gastroernterol Clin Biol 2002 and Textbook of Hepatology new edition 2007). The centrilobular predominance of hepatocellular necrosis may be consistent of drug induced injury. However, the number of examples with such features, without significant inflammatory infiltration is finally very limited, mainly paracetamol overdosage or directly toxic compounds or mushroom. Indeed, in these cases, the pattern is a kind of biochemical hepatectomy related to the acute but very short exposure to a toxic agent. This may explain the rapid improvement of liver enzymes and renal condition provided the lesion is not too severe and if there are no other aggravating factors.

In case of acute ischemia in a patient with normal heart function, there is a relatively good prognosis even for extensive lesion. In contrast, when the cardiac function is limited combining ischemia and stasis because of right cardiac failure, this may trigger an irreversible decompensation usually fatal. It is the picture that we can observe in this case. The liver and kidney samples obtained at the time of autopsy (11 days after the first event) mainly showed signs of circulatory failure. The autopsy revealed that the right heart ventricle was much deteriorated (ICU opinion) so that cardiac failure is the very likely cause of death (ICU opinion).

It would be very important that (b) (6) may review also the cardiac macroscopy and histology.

I agree that the role of the study drug cannot be excluded.

(b) (6).

Statement dated (b) (4)

Liver

The lobular architecture is intact, with the usual relation between portal tracts and central veins. Severe centrilobular necrosis and hemorrhage is present, but inflammation is sparse. Moderate macrovesicular steatosis is noted. The portal tracts appear normal.

Impression: The morphologic appearance is consistent with toxic liver injury of the predictable type. Such toxins include carbon tetrachloride, acetaminophen and poisonous mushrooms. The pathologic changes also resemble those seen in patients who have experienced profound shock, although those lesions are usually not as severe. The term ischemic hepatitis has also been employed. Clinical correlation is recommended.

Statement date (b) (4)

According to the clinical records, on (b) (6) the patient was conscious and oriented, with a Glasgow score of 15. Her blood pressure was 110/80 and the oxygen saturation was 98%. She had regular heart sounds and moderate tachycardia. Nevertheless, she was clearly in acute liver failure and suffered from renal insufficiency. Total bilirubin was 68. Platelets were 89,000, with abnormally high D-Dimers.

The clinical and laboratory data are not consistent with hemorrhagic centrilobular necrosis of the liver secondary to shock. Such lesions usually follow severe and sustained hypotension, which was not present in this case at the time of acute liver failure. A diagnosis of drug-induced toxic injury of the liver is far more likely. Please feel free to call upon me for any further information.

Dr. W. Maddrey, Clinical, U.S (b) (4)

Conclusion: All evidence supports ischemic hepatitis occurring in a patient with chronic heart failure and severe asthma who had a superimposed pulmonary embolization event. I could not find documentation of an episode of definite hypotension although I suspect such occurred. The patient had required dobutamine further supporting the conclusion of severe circulatory collapse. I do not think the study drug had a role in causing the hepatic injury.

7.3.4.4.4 Summary

The following table summarizes the number of cases with ALT >3xULN concurrent with TB>2xULN in all completed studies. There were 14 (0.15%) cases in the rivaroxaban group and 9 (0.13%) in the control group. In RECORD phase 3 trials, 7 cases (0.11%) in the rivaroxaban group and 3 (0.05%) in the enoxaparin group were considered to be possibly related to rivaroxaban by at least one member of the Liver Advisory Panel. Two of 14 subjects in the rivaroxaban group subsequently died with liver failure as compared to none in the enoxaparin group. One death was considered to be drug-induced cholestasis. Another death was considered

to be hepatitis B infection but the autopsy findings of liver tissues raised concerns for possible toxic origin of lesions. In both cases, the role of rivaroxaban could not be excluded.

An additional 27 cases of ALT >3xULN concurrent with TB >2xULN were reported in 5 ongoing studies. These included 4 cases in subjects who received rivaroxaban, 3 in subjects who received placebo, and 3 in subjects who received warfarin, 1 in subjects who received enoxaparin, and 16 still blinded cases. One subject in the rivaroxaban group in ongoing studies died with liver failure and the autopsy findings again raised liver advisory panel member concerns of likely drug-induced toxic injury.

In the RECORD studies, serious treatment-emergent ALT increased was reported more often in the rivaroxaban group (17, 0.27%) as compared to the enoxaparin group (11, 0.18%) although the rate of ALT>3x ULN was lower with rivaroxaban (152, 2.48%) than with enoxaparin (227, 3.70%). Because enoxaparin control has been known to cause benign liver enzyme elevation and such elevations are fully reversible (NDA 20-164, Lovenox labeling), the comparison of liver enzyme elevation between the two treatments would not eliminate the concerns of possible serious liver toxicity for rivaroxaban.

Previous experience with EXANTA (ximelagatran) that causes drug-induced liver injury suggested even short term tolerance does not necessarily predict long term safety (NDA 21-686, Medical Review, Dr. Ruyi He, M.D., 9/27/04; Cardiovascular and Renal Drug Advisory Committee Transcript, 9/10/04). In the current application, 92% of study patients were exposed to <35 days of rivaroxaban treatment and only 6% (635 patients) were exposed to rivaroxaban for 3 months based on completed studies. Therefore, the long-term safety data from ongoing studies, using a control that has not been shown to increase liver enzymes, such as warfarin, will be needed to fully evaluate the hepatotoxicity for rivaroxaban.

ALT >3x ULN Concurrent With TB>2x ULN in Completed Studies

	Rivaroxaban	**Control**
RECORD 1-4 Possible related	9/6131 (0.15%) 7/6131 (0.11%)	7/6131 (0.11%) 3/6131 (0.05%)
Phase 2 VTE Prophylaxis Studies	4/1700 (0.2%)	2/379 (0.5%)
Phase 2 VTE Treatment Studies	1/824 (0.1%)	0/235 (0%)
Phase 2 Atrial Fibrillation Studies	0/158 (0%)	0/76 (0%)
Phase 1 Studies	0/497 (0%)	0/180 (0%)

Total Liver-related deaths	14 /9310 (0.15%) 2/9310 (0.02%)	9/7001 (0.13%) 0

7.3.5 Submission Specific Primary Safety Concerns

Hepatic adverse events were discussed in the above section.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following table presents the common treatment-emergent adverse events reported in ≥2% of subjects in the rivaroxaban group in RECORD 1-4 Studies. Overall, there were 68% of rivaroxaban subjects and 69% of enoxaparin subjects who reported at least one treatment-emergent adverse event. The most frequent events occurring at an incidence of at least 2% of subjects were: nausea (788[12.7%] rivaroxaban and 797 [12.9%] enoxaparin subjects); pyrexia (719 [11.6%] rivaroxaban and 712 [11.5%] enoxaparin subjects); vomiting (605 [9.8%] rivaroxaban and 610 [9.8%] enoxaparin subjects); constipation (573 [9.3%] rivaroxaban and 596 [9.6%] enoxaparin subjects), and deep vein thrombosis (258 [4.2%] rivaroxaban and 450 [7.3%] enoxaparin subjects).

Adverse events that were reported more frequently on rivaroxaban compared to enoxaparin were peripheral edema, dizziness, pruritus, pain in extremity, urinary retention, muscle spasms, and wound secretion. Adverse events reported more frequently on enoxaparin compared to rivaroxaban were chest pain, ALT increase, AST increase, GGT increase, arthralgia, and DVT.

Common AEs that occurred ≥2% in the Rivaroxaban group in RECORD 1-4 Studies

Preferred Term	**Rivaroxaban (N=6183)**	**Enoxaparin (N=6200)**
Any AEs	4179 (67.59%)	4306 (69.45%)
Nausea	788 (12.74%)	797 (12.85%)
Pyrexia	719 (11.63%)	712 (11.48%)
Vomiting	605 (9.78%)	610 (9.84%)
Constipation	573 (9.27%)	596 (9.61%)
Peripheral edema	419 (6.78%)	409 (6.60%)
Anemia postoperative	352 (5.69%)	355 (5.73%)
Procedural pain	322 (5.21%)	345 (5.56%)
Hypotension	313 (5.06%)	315 (5.08%)
Insomnia	307 (4.97%)	326 (5.26%)
Dizziness	259 (4.19%)	243 (3.92%)
Deep vein thrombosis	258 (4.17%)	450 (7.26%)

Anemia	244 (3.95%)	244 (3.94%)
Pruritus	225 (3.64%)	202 (3.26%)
Pain in extremity	203 (3.28%)	167 (2.69%)
Diarrhea	158 (2.56%)	182 (2.94%)
Hemoglobin decreased	157 (2.54%)	166 (2.68%)
Urinary retention	156 (2.52%)	149 (2.40%)
Headache	153 (2.47%)	151 (2.44%)
Muscle spasms	148 (2.39%)	115 (1.85%)
Tachycardia	146 (2.36%)	149 (2.40%)
Wound secretion	146 (2.36%)	106 (1.71%)
ALT increased	134 (2.17%)	183 (2.95%)

7.4.2 Laboratory Findings

Laboratory safety data from the 2 THR studies (RECORD 1 and 2) and 2 TKR studies (RECORD 3 and 4) are presented separately since the testing schedule was slightly different. The following table shows the incidence of high (>1xULN) non-liver-related abnormalities in the THR and TKR studies, respectively.

Rivaroxaban and enoxaparin were generally similar with respect to showing elevations in laboratory abnormalities except for creatinine and urea. The incidences of high creatinine and urea abnormalities were higher on rivaroxaban compared to enoxaparin (based on treatment-emergent analysis). This pattern was present in the hip replacement studies (RECORD 1 and 2) and the knee replacement studies (RECORD 3 and 4). It was also noted that the incidence of high amylase was slightly higher with rivaroxaban than with enoxaparin in both hip and knee replacement studies.

Pooled Treatment-emergent Incidence Rates of High (>1x ULN) Laboratory Abnormalities[a] (Subjects Valid for Safety in RECORD 1 and 2)

Category Laboratory Variable	Rivaroxaban (N=3437)		Enoxaparin (N=3453)	
Hematology				
Hematocrit	5/3300	(0.15%)	8/3307	(0.24%)
Hemoglobin	6/3318	(0.18%)	6/3321	(0.18%)
White blood cells	1861/3072	(60.58%)	1891/3115	(60.71%)
Neutrophils (total)	1567/1906	(82.21%)	1568/1907	(82.22%)
Lymphocytes	83/2085	(3.98%)	109/2090	(5.22%)
Monocytes	467/1950	(23.95%)	465/1952	(23.82%)
Eosinophils	333/1955	(17.03%)	330/1967	(16.78%)
Basophils	166/2018	(8.23%)	150/2020	(7.43%)
Platelets	1995/3191	(62.52%)	1976/3200	(61.75%)
Blood Chemistry				
Glucose, unspecified	1105/3056	(36.16%)	1062/3039	(34.95%)
Uric Acid	92/3219	(2.86%)	92/3213	(2.86%)
Calcium	32/3318	(0.96%)	43/3323	(1.29%)
Sodium	22/3353	(0.66%)	17/3366	(0.51%)
Potassium	152/3289	(4.62%)	148/3286	(4.50%)
Creatinine	291/2819	(10.32%)	224/2789	(8.03%)
Urea	287/3107	(9.24%)	231/3079	(7.50%)
Albumin	0/3366	(0%)	0/3380	(0%)
Lactate dehydrogenase	1440/3153	(45.67%)	1560/3177	(49.10%)
Amylase	508/3086	(16.46%)	477/3090	(15.44%)
Lipase	438/3104	(14.11%)	416/3112	(13.37%)

[a] High is above upper limit of normal
Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the highest value up to and including Day 0 is used as baseline.
Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the abnormality post-baseline
at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline
Note: Measurements taken mare than 2 days after stop of double-blind treatment are not included

Pooled Treatment-emergent Incidence Rates of High (>1x ULN) Laboratory Abnormalities[a]
(Subjects Valid for Safety in RECORD 3 and 4)

Category Laboratory Variable	Rivaroxaban (N=2746)		Enoxaparin (N=2747)	
Hematology				
Hematocrit	2/2631	(0.08%)	1/2609	(0.04%)
Hemoglobin	2/2639	(0.08%)	2/2628	(0.08%)
White blood cells	1301/2506	(51.92%)	1334/2514	(53.06%)
Neutrophils (total)	1329/1887	(70.43%)	1310/1869	(70.09%)
Lymphocytes	30/1952	(1.54%)	31/1939	(1.60%)
Monocytes	265/1883	(14.07%)	281/1857	(15.13%)
Eosinophils	210/1844	(11.39%)	226/1799	(12.56%)
Basophils	81/1949	(4.16%)	75/1921	(3.90%)
Platelets	1615/2567	(62.91%)	1574/2546	(61.82%)
Blood Chemistry				
Glucose, unspecified	912/2322	(39.28%)	942/2347	(40.14%)
Uric Acid	76/2525	(3.01%)	73/2504	(2.92%)
Calcium	14/2646	(0.53%)	25/2635	(0.95%)
Sodium	22/2668	(0.82%)	25/2664	(0.94%)
Potassium	151/2623	(5.76%)	137/2625	(5.22%)
Creatinine	280/2163	(12.94%)	248/2146	(11.56%)
Urea	234/2428	(9.64%)	188/2424	(7.76%)
Albumin	0/2691	(0%)	0/2690	(0%)
Lactate dehydrogenase	1611/2404	(67.01%)	1628/2413	(67.47%)
Amylase	285/2451	(11.63%)	263/2454	(10.72%)
Lipase	321/2485	(12.92%)	318/2500	(12.72%)

[a] High is above upper limit of normal
Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the highest value up to and including Day 0 is used as baseline.
Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the abnormality post-baseline
at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline
Note: Measurements taken mare than 2 days after stop of double-blind treatment are not included

The following tables show the frequency of creatinine and urea abnormalities >1x, 1.5x, and 2x ULN at specified time points. The Day 0 laboratory assessment was done on the day prior to surgery. The Day 1 laboratory assessment was done on the day of surgery (after surgery but prior to first tablet intake). After Day 1, the assessments reflect laboratory assessments made on study drug at any time through the follow-up period. The tables below include all subjects regardless of whether they had a baseline abnormality or not (post-baseline analysis).

In THR studies, after Day 1, the frequency of creatinine abnormalities was comparable in both groups but the frequency of urea abnormalities remained higher in the rivaroxaban group than the enoxaparin group (see table below). However, there were more subjects with creatinine and urea abnormalities at baseline and at Day 1 in the enoxaparin group than in the rivaroxaban group. The similar prevalence of creatinine abnormalities between the two groups after Day 1 further confirms a higher incidence of creatinine and urea abnormalities with rivaroxaban than with enoxaparin.

Creatinine and Urea Postbaseline Laboratory Abnormalities by Time Windows and Visits (Subjects Valid for Safety in RECORD 1 and 2)

Laboratory Abnormality	Rivaroxaban		Enoxaparin	
Visit/Time Window	N/D	(%)	N/D	(%)
Creatinine >1x ULN				
Day 0	556/3411	(16.30%)	604/3433	(17.59%)
Day 1	191/3344	(5.71%)	244/3354	(7.27%)
After Day 1	683/3361	(20.32%)	680/3347	(20.32%)
Creatinine >1.5x ULN				
Day 0	38/3411	(1.11%)	55/3433	(1.60%)
Day 1	12/3344	(0.36%)	26/3354	(0.78%)
After Day 1	82/3361	(2.44%)	81/3347	(2.42%)
Creatinine >2x ULN				
Day 0	9/3411	(0.26%)	11/3433	(0.32%)
Day 1	3/3344	(0.09%)	3/3354	(0.09%)
After Day 1	24/3361	(0.71%)	28/3347	(0.84%)
Urea >1x ULN				
Day 0	262/3411	(7.68%)	314/3435	(9.14%)
Day 1	65/3344	(1.94%)	85/3354	(2.53%)
After Day 1	477/3361	(14.19%)	443/3347	(13.24%)
Urea >1.5x ULN				
Day 0	15/3411	(0.44%)	23/3435	(0.67%)
Day 1	5/3344	(0.15%)	4/3354	(0.12%)
After Day 1	58/3361	(1.73%)	54/3347	(1.61%)
Urea >2x ULN				
Day 0	5/3411	(0.15%)	1/3435	(0.03%)
Day 1	2/3344	(0.06%)	0/3354	(0.00%)
After Day 1	14/3361	(0.42%)	7/3347	(0.21%)

Key: D = denominator; N = numerator; ULN = upper limit of normal

In the TKR studies, after Day 1, the frequency of creatinine and urea abnormalities in all categories except urea >2x ULN remained higher on rivaroxaban compared with enoxaparin (see Table below). Again, it was noted that there were more subjects with creatinine and urea abnormalities at baseline and at Day 1 in the enoxaparin group than in the rivaroxaban group. This further confirms a higher incidence of creatinine and urea abnormalities with rivaroxaban than with enoxaparin.

Creatinine and Urea Postbaseline Laboratory Abnormalities by Time Windows and Visits (Subjects Valid for Safety in RECORD 3 and 4)

Laboratory Abnormality	Rivaroxaban		Enoxaparin	
Visit/Time Window	N/D	(%)	N/D	(%)
Creatinine >1x ULN				
Day 0	534/2721	(19.63%)	556/2723	(20.42%)
Day 1	277/2669	(10.38%)	296/2668	(11.09%)
After Day 1	722/2673	(27.01%)	683/2666	(25.62%)
Creatinine >1.5x ULN				
Day 0	62/2721	(2.28%)	45/2723	(1.65%)
Day 1	22/2669	(0.82%)	20/2668	(0.75%)
After Day 1	105/2673	(3.93%)	90/2666	(3.38%)
Creatinine >2x ULN				
Day 0	5/2721	(0.18%)	7/2723	(0.26%)
Day 1	3/2669	(0.11%)	2/2668	(0.07%)
After Day 1	25/2673	(0.94%)	22/2666	(0.83%)
Urea >1x ULN				
Day 0	267/2721	(9.81%)	274/2723	(10.06%)
Day 1	93/2669	(3.48%)	101/2668	(3.79%)
After Day 1	445/2673	(16.65%)	392/2666	(14.70%)
Urea >1.5x ULN				
Day 0	26/2721	(0.96%)	19/2723	(0.70%)
Day 1	10/2669	(0.37%)	10/2668	(0.37%)
After Day 1	57/2673	(2.13%)	53/2666	(1.99%)
Urea >2x ULN				
Day 0	3/2721	(0.11%)	3/2723	(0.11%)
Day 1	1/2669	(0.04%)	1/2668	(0.04%)
After Day 1	16/2673	(0.60%)	16/2666	(0.60%)

Key: D = denominator; N = numerator; ULN = upper limit of normal

In the pooled RECORD studies, any serious treatment-emergent "renal and urinary disorders" was reported in 13 (0.21%) and 10 (0.16%) subjects on rivaroxaban and enoxaparin, respectively. Serious "renal failure acute" was reported in 6 (0.10%) and 5 (0.08%) subjects on rivaroxaban and enoxaparin, respectively. Serious "renal failure" was reported in 0 and 2 (0.03%) subjects on rivaroxaban and enoxaparin, respectively. Serious "renal impairment" was reported in 1 (0.02%) and 0 subjects on rivaroxaban and enoxaparin, respectively. Serious "urinary retention" was reported in 4 (0.06%) and 0 subjects on rivaroxaban and enoxaparin. Serious 'hematuria" was reported in 1 (0.02%) and 0 subjects on rivaroxaban and enoxaparin.

In the RECORD studies, any treatment-emergent "renal and urinary disorders" was reported in 333 (5.39%) and 309 (4.98%) subjects on rivaroxaban and enoxaparin, respectively. The most frequent adverse events reported more with rivaroxaban than with enoxaparin were urinary retention [156 (2.52%) and 149 (2.40%)], dysuria [55(0.89%) and 33(0.53%)], hematuria [33 (0.53%) and 16 (0.26%)], pollakiuria [30 (0.49%) and 25 (0.40%)], urogenital hemorrhage [4 (0.06%) and 0 (0.00%)], and renal impairment [3 (0.05%) and 1 (0.02%)] for rivaroxaban and enoxaparin, respectively. The term "renal failure" was reported in 1 (0.02%) and 7 (0.11%) subjects on rivaroxaban and enoxaparin, respectively. "Renal failure acute" was reported in 6 (0.10%) and 8 (0.13%) subjects on rivaroxaban and enoxaparin, respectively.

The following tables show the incidence of low (<1x LLN) non-liver-related abnormalities in the THR and TKR studies, respectively. Rivaroxaban and enoxaparin were generally similar with respect to occurrence of low laboratory abnormalities.

Pooled Treatment-emergent Incidence Rates of Low (<1x LLN) Laboratory Abnormalities[a] (Subjects Valid for Safety in RECORD 1 and 2)

Category Laboratory Variable	Rivaroxaban (N=3437)		Enoxaparin (N=3453)	
Hematology				
Hematocrit	2478/2629	(94.26%)	2537/2679	(94.70%)
Hemoglobin	2575/2750	(93.64%)	2649/2810	(94.27%)
White blood cells	118/3291	(3.59%)	128/3291	(3.89%)
Neutrophils (total)	64/2039	(3.14%)	96/2061	(4.66%)
Lymphocytes	1648/1935	(85.17%)	1619/1925	(84.10%)
Monocytes	377/1889	(19.96%)	406/1895	(21.42%)
Eosinophils	535/910	(58.79%)	556/905	(61.44%)
Basophils	94/179	(52.51%)	92/178	(51.69%)
Platelets	339/3278	(10.34%)	345/3274	(10.54%)
Blood Chemistry				
Glucose, unspecified	156/3318	(4.70%)	149/3333	(4.47%)
Uric Acid	459/3288	(13.96%)	516/3321	(15.54%)
Calcium	2502/3293	(75.98%)	2525/3320	(76.05%)
Sodium	321/3299	(9.73%)	278/3300	(8.42%)
Potassium	297/3264	(9.10%)	330/3297	(10.01%)
Creatinine	453/3282	(13.80%)	517/3298	(15.68%)
Urea	43/3366	(1.28%)	35/3371	(1.04%)
Albumin	1242/3356	(37.01%)	1272/3373	(37.71%)
Lactate dehydrogenase	65/3303	(1.97%)	59/3313	(1.78%)
Amylase	381/3275	(11.63%)	393/3280	(11.98%)
Lipase	110/3357	(3.28%)	94/3371	(2.79%)

[a] Low is below lower limit of normal

Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the lowest value up to and including Day 0 is used as baseline.

Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the abnormality post-baseline
at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline

Note: Measurements taken more than 2 days after stop of double-blind treatment are not included

Note: Hematology lab tests were done locally and therefore the LLN could vary from site to site. If the LLN includes 0, a subject would not be considered evaluable in a treatment-emergent analysis of low laboratory abnormalities. Consequently the denominator for certain lab tests (i.e. basophils) are markedly lower than for other lab tests.

Pooled Treatment-emergent Incidence Rates of Low (<1x LLN) Laboratory Abnormalities[a] (Subjects Valid for Safety in RECORD 3 and 4)

Category Laboratory Variable	Rivaroxaban (N=2746)		Enoxaparin (N=2747)	
Hematology				
Hematocrit	1930/2107	(91.60%)	1987/2143	(92.72%)
Hemoglobin	1997/2180	(91.61%)	2026/2202	(92.01%)
White blood cells	44/2624	(1.68%)	70/2594	(2.70%)
Neutrophils (total)	38/1959	(1.94%)	29/1938	(1.50%)
Lymphocytes	1336/1846	(72.37%)	1336/1818	(73.49%)
Monocytes	275/1622	(16.95%)	296/1622	(18.25%)
Eosinophils	364/839	(43.38%)	399/823	(48.48%)
Basophils	32/112	(28.57%)	35/109	(32.11%)
Platelets	170/2616	(6.50%)	173/2608	(6.63%)
Blood Chemistry				
Glucose, unspecified	112/2603	(4.30%)	102/2604	(3.92%)
Uric Acid	260/2659	(9.78%)	265/2667	(9.94%)
Calcium	1635/2642	(61.88%)	1685/2634	(63.97%)
Sodium	439/2618	(16.77%)	451/2641	(17.08%)
Potassium	317/2610	(12.15%)	314/2594	(12.10%)
Creatinine	189/2657	(7.11%)	216/2664	(8.11%)
Urea	27/2688	(1.00%)	38/2689	(1.41%)
Albumin	656/2688	(24.40%)	657/2688	(24.44%)
Lactate dehydrogenase	20/2670	(0.75%)	26/2655	(0.98%)
Amylase	422/2599	(16.24%)	459/2594	(17.69%)
Lipase	133/2680	(4.96%)	132/2680	(4.93%)

[a] Low is below lower limit of normal
Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the lowest value up to and including Day 0 is used as baseline.
Note: Incidence rate = # of events / # at risk, where:
# of events = # of subjects reporting the abnormality post-baseline
at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline
Note: Measurements taken more than 2 days after stop of double-blind treatment are not included

Laboratory parameters of special interest were lipase and platelets.

Lipase was of interest in the Phase 3 RECORD program because the Phase 2 orthopedic surgery database suggested a trend towards an increased incidence of lipase and amylase laboratory abnormalities relative to enoxaparin. The following table shows that the incidences of lipase abnormalities at various thresholds (e.g. >3, >5, >8x ULN) are generally similar between rivaroxaban and enoxaparin groups. The incidence of "lipase increased" reported as an adverse event by investigators was 50 (0.81%) versus 45 (0.73%) subjects on rivaroxaban and enoxaparin, respectively. The adverse event term "pancreatitis" occurred in 1 (<0.1%) and 2 (<0.1%) rivaroxaban and enoxaparin subjects, respectively. The incidence of the adverse event term "acute pancreatitis" occurred in 1 (<0.1%) and 3 (<0.1%) rivaroxaban and enoxaparin subjects, respectively.

The incidences of low platelet abnormalities at various thresholds (e.g. < 30, < 50, < 80 or < 100) are generally similar between rivaroxaban and enoxaparin, respectively (see Table below). "Platelet count decreased" reported as an adverse event occurred in 7 (0.1%) and 7(0.1%) rivaroxaban and enoxaparin subjects, respectively.

Incidence Rates of Prespecified Treatment-emergent Laboratory Abnormalities (Subjects Valid for Safety in pooled RECORD 1-4 studies)

Laboratory Variable Limit	Rivaroxaban (N=6183)		Enoxaparin (N=6200)	
	N/D	%	N/D	%
Lipase				
>3x ULN	137/6061	(2.26%)	152/6082	(2.50%)
>5x ULN	70/6073	(1.15%)	83/6088	(1.36%)
>8x ULN	43/6076	(0.71%)	45/6090	(0.74%)
Platelets				
<30 GIGA/L	3/6040	(0.05%)	4/6033	(0.07%)
<50 GIGA/L	6/6039	(0.10%)	7/6032	(0.12%)
<80 GIGA/L	32/6032	(0.53%)	29/6024	(0.48%)
<100 GIGA/L or <baseline/2	152/6023	(2.52%)	157/6015	(2.61%)

Key: ULN = upper limit of normal; N = numerator, D = denominator
Note: The schedule Day 0 visit is used as baseline. If earlier visits are present, the lowest value up to and including Day 0 is used as baseline.
Note: Incidence rate = # of events / # at risk, where # of events = # of subjects reporting the abnormality post-baseline # at risk = # of subjects with baseline and post-baseline readings who did not report the abnormality at baseline
Note: All measurements after the start of study medication are included regardless of onset relative to the last dose of study medication.

7.4.3 Vital Signs

Vital sign data from the 2 THR studies and 2 TKR studies are presented separately in the following table since the testing schedule was slightly different. The effects of rivaroxaban and enoxaparin on systolic blood pressure, diastolic blood pressure, and heart rate are generally similar.

Vital Sign Measurements[a]
(Subjects Valid for Safety in Pooled RECORD 1 & 2, and Pooled RECORD 3 & 4)

Study Parameter Change period	Rivaroxaban		Enoxaparin	
RECORD 1 and 2	N	Mean ± SD	N	Mean ± SD
Diastolic BP (mm Hg)				
Baseline	3397	80.26 ± 10.13	3415	80.43 ± 9.93
Change from baseline (Day 1)	3384	-8.90 ± 13.64	3406	-9.21 ± 13.55
Change from baseline (Day 6[b])	3269	-5.99 ± 11.83	3276	-5.93 ± 11.26
Change from baseline (Day 13[b])	3186	-4.28 ± 11.47	3174	-4.25 ± 11.52
Change from baseline (Day 65[c])	3026	-0.53 ± 12.01	3012	-0.50 ± 11.50
Systolic BP (mm Hg)				
Baseline	3397	136.11 ± 18.23	3415	136.5 ± 17.98
Change from baseline (Day 1)	3385	-12.59 ± 21.51	3406	-13.24 ± 21.57
Change from baseline (Day 6)	3270	-8.62 ± 18.59	3277	-8.29 ± 18.09
Change from baseline (Day 13)	3186	-7.39 ± 18.30	3175	-7.76 ± 18.06
Change from baseline (Day 65)	3027	-2.43 ± 18.40	3012	-2.77 ± 18.17
Heart rate (bpm)				
Baseline	3381	73.50 ± 9.78	3402	73.77 ± 10.04
Change from baseline (Day 1)	3363	1.07 ± 12.69	3389	0.85 ± 12.85
Change from baseline (Day 6)	3245	3.69 ± 11.20	3254	3.34 ± 11.57
Change from baseline (Day 13)	3167	2.54 ± 10.80	3147	2.20 ± 11.12
Change from baseline (Day 65)	3016	1.38 ± 10.78	3005	1.11 ± 10.73
RECORD 3 and 4				
Diastolic BP (mm Hg)				
Baseline	2724	79.76 ± 10.16	2724	79.93 ± 10.37
Change from baseline (Day 1)	2718	-7.19 ± 13.47	2721	-7.17 ± 13.77
Change from baseline (Day 6)	2613	-5.52 ± 11.76	2601	-5.46 ± 12.18
Change from baseline (Day 13)	2532	-3.03 ± 11.61	2527	-3.02 ± 11.87
Change from baseline (Day 42)	2474	-0.91 ± 11.19	2464	-1.01 ± 11.92
Systolic BP (mm Hg)				
Baseline	2724	136.54 ± 17.09	2724	136.67 ± 17.66
Change from baseline (Day 1)	2718	-8.28 ± 21.35	2721	-8.11 ± 21.76
Change from baseline (Day 6)	2613	-5.90 ± 18.71	2601	-6.06 ± 18.96
Change from baseline (Day 13)	2532	-4.36 ± 18.44	2527	-4.51 ± 18.47
Change from baseline (Day 42)	2474	-3.21 ± 18.14	2464	-3.03 ± 18.54
Heart rate (bpm)				
Baseline	2723	74.48 ± 10.26	2716	74.00 ± 10.51
Change from baseline (Day 1)	2714	0.31 ± 13.27	2711	0.82 ± 13.22
Change from baseline (Day 6)	2610	4.58 ± 12.40	2593	5.15 ± 12.64
Change from baseline (Day 13)	2525	3.14 ± 11.73	2517	3.51 ± 12.08
Change from baseline (Day 42)	2467	2.21 ± 11.23	2460	2.39 ± 11.54

[a] Vital sign measurements in subjects with at least 1 baseline and 1 postbaseline vital signs assessment.
[b] (± 2 days)
[c] (± 5days)
Key: BP = blood pressure; od = once daily
Note: Day 0 visit is used as baseline.
Note: Since more than 1 measurement is available for a subject at the same visit (postbaseline), the mean value is used for analysis.

7.4.4 Electrocardiograms (ECGs)

Routine electrocardiographic safety monitoring was not done in the Phase 3 RECORD studies. A thorough Phase 1 QT study (Study 11275) was performed and is being reviewed by Clinical Pharmacology reviewer.

7.4.5 Special Safety Studies

N/A

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the Phase 2 orthopedic VTE prophylaxis dose-ranging studies there was an increased risk of bleeding events with increasing rivaroxaban dose. No non-bleeding events appeared to be related to rivaroxaban dose. Only one dose of rivaroxaban was studied in the phase 3 trials.

7.5.2 Time Dependency for Adverse Events

No specific time of dependency for adverse events was clearly identified.

7.5.3 Drug-Demographic Interactions

According to subgroup analysis, in certain subgroups, such as Asian subjects, subjects with body weight ≤50 kg or >110 kg, BMI<18.5 or ≥40, the risk of major or non-major clinically relevant bleeding event appears to be higher with rivaroxaban as compared to other groups.

In the RECORD phase 3 trials, it was noted that there was a significantly higher incidence of ALT>3xULN and TB>2xULN in the rivaroxaban group (4, 0.65%) than in the enoxaparin group (1, 0.16%) in Asians. The four Asians in the rivaroxaban group were from China, Indonesia, India and Sri Lanka. The one Asian in enoxaparin group was from India. There were also higher incidences of ALT>10 xULN and >20xULN with rivaroxaban than with enoxaparin in Asians. The differences between the two treatment groups for Asians were not seen for other liver-related abnormalities. Further investigation is needed to determine if Asians are more susceptible to possible liver injury with rivaroxaban.

7.5.4 Drug-Disease Interactions

Hepatic impairment:

A phase 1 study in subjects with Child Pugh A and B was conducted and is under review by Clinical pharmacology. According to the sponsor, the study showed no difference in pharmacokinetic or pharmacodynamic response in healthy subjects compared to subjects classified as Child Pugh A. Subjects classified as Child Pugh B had more pronounced pharmacokinetic and pharmacodynamic effects. Subjects classified as Child Pugh C were not studied in Phase 1 studies.

In the Phase 3 RECORD studies, subjects with significant liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis) were to be excluded from enrollment. However, some subjects with elevated liver enzymes (e.g. ALT or AST) were enrolled. There were no apparent differences in liver safety for the subjects entering the trial with elevated ALT or AST values compared with those with normal values.

One rivaroxaban subject with HBsAg positive at baseline detected by retention sample in a phase 2 trial developed fulminant liver failure and subsequently died. Another rivaroxaban subject in phase 3 RECORD trial was diagnosed with hepatitis C by serology tests. Because of the temporal association between rivaroxaban treatment and the occurrence of these events, concern is raised for possible virus activation by rivaroxaban treatment.

Renal impairment:

A phase 1 study in subjects with renal impairment was conducted and is under review by Clinical pharmacology.

Based on Clinical Pharmacology review, in subjects with mild (creatinine clearance 50 to <80 mL/min), moderate (creatinine clearance 30 to <50 mL/min) or severe renal impairment (creatinine clearance 15 to <30 mL/min) rivaroxaban plasma exposure (Cmax and AUC) was increased and the overall inhibition of FXa activity was increased by 1.5-, 1.9- and 2.0-fold respectively, compared to healthy subjects with normal renal function (creatinine clearance >80 mL/min). In addition, the increased overall exposure was associated with an increased sensitivity of prothrombin time prolongation. Patients with creatinine clearance <15 mL/min were not studied.

In the Phase 3 RECORD studies, subjects with a severe renal impairment were to be excluded from the studies. However, 57 subjects (29 in the rivaroxaban group and 28 in the enoxaparin group) with creatinine clearance <30 mL/min were enrolled in the Phase 3 RECORD studies. Major or non-major clinically relevant bleeding was reported in 3 (10.34%) subjects in the rivaroxaban group and 1 (3.57%) subjects in the enoxaparin group in patients with creatinine clearance <30 mL/min although the number of patients was relatively small in this subpopulation.

A total of 380 and 409 subjects with creatinine clearance 30 to <50 mL/min (moderate renal impairment) were included in the rivaroxaban and enoxaparin groups, respectively, of the RECORD studies. Major or non-major clinically relevant bleeding was reported in 10 (2.63%) subjects in the rivaroxaban group and 13 (3.18%) subjects in the enoxaparin group in patients with creatinine clearance 30 to <50 mL/min.

7.5.5 Drug-Drug Interactions

Phase 1 drug-drug interactions studies involving coadministration of rivaroxaban and ketoconazole, ritonavir, clarithromycin or erythromycin were conducted and are under review by clinical pharmacology.

Rivaroxaban is eliminated both metabolically (primarily CYP3A4 mediated) and renally (primarily active secretion).

In the 4 RECORD studies the influence of 6 classes of co-medication use (CYP3A4 or P-gp inhibitors, NSAIDs, opioid, statin, nitrate and antiplatelet agents) on post-tablet major or non-major clinically relevant bleeding event and any bleeding event rates per 100 patient-weeks for rivaroxaban and enoxaparin was explored.

In pooled RECORD studies, there were about 70% of study patients on NSAIDs, 94% on opioids, 18% on statins, 4% on nitrates, 9% on patelet aggregation inhibitors or ASA, and 8% on CYP-3A4 or P-gp inhibitors. The number of subjects with use of these co-medications between the day of surgery and the end of the risk period is well balanced for the rivaroxaban and enoxaparin/placebo group (see Table below).

Number and Proportion (%) of Subjects with Use [a] of Co-medication In RECORD 1, 2, 3, and 4 Pool (Safety Population with Surgery and Tablet Intake)

Concomitant Drug(s)	Rivaroxaban 10 mg od (N=6093)	Enoxaparin / Placebo (N=6107)
NSAIDs	4396 (72%)	4432 (73%)
Opioids	5714 (94%)	5740 (94%)
Statins	1092 (18%)	1028 (17%)
Nitrates	260 (4%)	283 (5%)
Platelet aggregation inhibitors or ASA	563 (9%)	526 (9%)
CYP-3A4 or P-gp inhibitors	467 (8%)	465 (8%)

a Time under concomitant drug use or up to 2 days after last intake of concomitant drug considered time of co-medication use

The analyses focus on treatment emergent adjudicated bleeding events ('major and non-major clinically relevant' and 'any bleeding') after first tablet intake (rivaroxaban or matching placebo). The at-risk period for which bleeding events and person time are accumulated, extends from the day of surgery until the last day of study medication intake + 2 days or event onset date, whatever is first. The use of co-medications is a time-dependent covariate and a subject may be on and off the co-medications of interest in the evaluated risk period. If a subject experienced a

bleeding event while receiving the listed co-medication (up to 2 days after co-medication discontinuation), the event would be counted as occurring with co-medication use. If an event occurred while a subject was not taking the listed co-medication, the event would be counted as occurring without co-medication use. The table also includes data on the proportion of patient-time accumulated by subjects using the listed co-medication relative to the total time of rivaroxaban exposure.

The following table presents the proportion of person-time within the three time intervals "day 1-3", "day 4-7" and ">day 7" and the overall risk period. It shows that the proportion of NSAID and Opioid exposed person-time decreases over time, while the proportion of exposed person-time is more constant over time for the other 4 drug classes.

Proportion of Person-Time with Use of Co-medication in Time Windows after Surgery RECORD 1, 2, 3, and 4 Pool (Safety Population with Surgery and Tablet Intake)

Concomitant Drug(s) / Treatment Group	Day 1 - 3	Day 4 – 7	After Day 7	Total Risk Period
Total Number of Patient-Weeks at Risk [a]				
Rivaroxaban 10 mg od	2593	3321	15717	21631
Enoxaparin / Placebo	2602	3329	15621	21552
Proportion (%) of Person Time [b] with Concomitant Use of				
NSAIDs				
Rivaroxaban 10 mg od	62%	51%	29%	36%
Enoxaparin / Placebo	62%	52%	28%	36%
Opioids				
Rivaroxaban 10 mg od	91%	60%	26%	39%
Enoxaparin / Placebo	92%	60%	27%	40%
Statins				
Rivaroxaban 10 mg od	17%	17%	14%	15%
Enoxaparin / Placebo	15%	16%	13%	14%
Nitrates				
Rivaroxaban 10 mg od	3%	3%	3%	3%
Enoxaparin / Placebo	4%	3%	2%	3%
Plat.Agg. Inhibitors or ASA				
Rivaroxaban 10 mg od	3%	4%	5%	5%
Enoxaparin / Placebo	3%	4%	4%	4%
CYP3A4 or P-gp inhibitors				
Rivaroxaban 10 mg od	7%	6%	4%	5%
Enoxaparin / Placebo	6%	6%	4%	5%

a Person time from analysis of any bleeding event.
b Time (at risk) under concomitant drug use or up to 2 days after last intake of concomitant drug considered time of co-medication use.

The following tables lists the number of subjects, major or clinically relevant non-major bleeding events, crude bleeding rate, as well as bleeding rate per patient time analysis for each co-medication use in the two treatment groups. It appears that the subjects with concomitant use of NSAIDs, opiods, statins, and nitrates experienced more major or clinically relevant non-major bleeding events than those without use of these medications in the rivaroxaban group, as well as in the enoxaparin group.

BAY 59-7939 (RIVAROXABAN) / PHASE III GLOBAL INTEGRATED ANALY
PREVENTION OF VENOUS THROMBOEMBOLISM
TABLE 14.3.5/10.1.1
INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND
WITH CO-MEDICATION: NSAID
POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PLA
POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: NSAID

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	4392	92	2.09	7981.3	1.15	(0.93, 1.41)
	NO	4956	81	1.63	14148.9	0.57	(0.45, 0.71)
ENOXAPARIN / PLACEBO	YES	4422	64	1.45	7938.3	0.81	(0.62, 1.03)
	NO	5027	66	1.31	14161.4	0.47	(0.36, 0.59)

BAY 59-7939 (RIVAROXABAN) / PHASE III GLOBAL INTEGRATED ANALY
PREVENTION OF VENOUS THROMBOEMBOLISM
TABLE 14.3.5/10.2.1
INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND
WITH CO-MEDICATION: OPIOID
POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PLA
POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: OPIOID

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	5714	130	2.28	8700.4	1.49	(1.25, 1.77)
	NO	4376	43	0.98	13429.7	0.32	(0.23, 0.43)
ENOXAPARIN / PLACEBO	YES	5738	93	1.62	8842.1	1.05	(0.85, 1.29)
	NO	4366	37	0.85	13257.6	0.28	(0.20, 0.38)

BAY 59-7939 (RIVAROXABAN) / PHASE III GLOBAL INTEGRATED ANALYSE
PREVENTION OF VENOUS THROMBOEMBOLISM
TABLE 14.3.5/10.3.1
INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND EX
WITH CO-MEDICATION: STATIN
POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PLACE
POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: STATIN

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	1091	39	3.57	3359.0	1.16	(0.83, 1.59)
	NO	5189	134	2.58	18771.1	0.71	(0.60, 0.85)
ENOXAPARIN / PLACEBO	YES	1028	24	2.33	3028.6	0.79	(0.51, 1.18)
	NO	5268	106	2.01	19071.1	0.56	(0.46, 0.67)

BAY 59-7939 (RIVAROXABAN) / PHASE III — GLOBAL INTEGRATED ANALYSE
PREVENTION OF VENOUS THROMBOEMBOLISM

TABLE 14.3.5/10.4.1

INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND EX
WITH CO-MEDICATION: NITRATE

POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PLACE
POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: NITRATE

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	258	8	3.10	663.6	1.21	(0.52, 2.37)
	NO	5932	165	2.78	21466.6	0.77	(0.66, 0.90)
ENOXAPARIN / PLACEBO	YES	283	7	2.47	586.7	1.19	(0.48, 2.46)
	NO	5962	123	2.06	21513.0	0.57	(0.48, 0.68)

BAY 59-7939 (RIVAROXABAN) / PHASE III — GLOBAL INTEGRATED ANALY
PREVENTION OF VENOUS THROMBOEMBOLISM

TABLE 14.3.5/10.6.1

INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND
WITH CO-MEDICATION: CYP3A4 OR P-GP INHIBITORS

POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PL
POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: CYP3A4 OR P-GP INHIBITORS

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	465	12	2.58	1068.9	1.12	(0.58, 1.96)
	NO	5830	161	2.76	21061.3	0.76	(0.65, 0.89)
ENOXAPARIN / PLACEBO	YES	464	2	0.43	1019.4	0.20	(0.02, 0.71)
	NO	5859	128	2.18	21080.3	0.61	(0.51, 0.72)

BAY 59-7939 (RIVAROXABAN) / PHASE III — GLOBAL INTEGRATED ANALY
PREVENTION OF VENOUS THROMBOEMBOLISM

TABLE 14.3.5/10.5.1

INCIDENCE RATES OF POST-TABLET MAJOR OR NON-MAJOR CLIN. RELEVANT BLEEDING PER 100 PAT.-WEEKS BY TREATMENT AND
WITH CO-MEDICATION: PLAT.AGGR. INIHIBITORS OR ASA

POPULATION: SUBJECTS VALID FOR SAFETY WITH SURGERY AND AT LEAST ONE DOSE OF BAY 59-7939 (TABLET/MATCHING PLA
POOL OF SN 11354 (RECORD 1), SN 11355 (RECORD 4), 11356 (RECORD 3) AND 11357 (RECORD 2)

CO-MEDICATION: PLAT.AGGR. INIHIBITORS OR ASA

TREATMENT	CO-MED.	NO. OF PAT.	NO. OF EVENTS	EVENT RATE (%)	PAT.-WKS AT RISK	RATE PER 100 PAT.-WKS ESTI-MATE	95% CI
RIVAROXABAN 10 MG OD	YES	554	8	1.44	1025.6	0.78	(0.34, 1.54)
	NO	5983	165	2.76	21104.6	0.78	(0.67, 0.91)
ENOXAPARIN / PLACEBO	YES	518	5	0.97	843.6	0.59	(0.19, 1.38)
	NO	6014	125	2.08	21256.1	0.59	(0.49, 0.70)

The following table shows the relative rate of major or non-major clinically relevant bleeding events in subjects using the listed co-medication relative to non-use in both the rivaroxaban and enoxaparin groups from the RECORD studies.

In the rivaroxaban group, it suggests that patients with concomitant use of opioid and statin had 2.5 and 1.5-fold higher risk of major or clinical relevant non-major bleeding, respectively, as compared to those without use of these medications. The relative rate with use of opioids versus no use for major or non-major clinically relevant bleeding was nearly 2 fold on rivaroxaban (2.52) compared to enoxaparin (1.31). The relative rate with use of statin versus no use major or non-major clinically relevant bleeding was also higher on rivaroxaban (1.52) compared to enoxaparin (1.26).

Patients with concomitant use of NSAIDs, nitrates, platelet aggregation inhibitors or ASA, and CYP3A4 or Pgp inhibitors also had a slightly higher rate of major or clinical relevant non-major bleeding as compared to those without use of these medications in the rivaroxaban group but the increase was not statistically significant.

For concomitant use of CYP3A4 or Pgp inhibitors, the relative rate of major or clinical relevant non-major bleeding with use versus no use was 5-fold higher on rivaroxaban group (1.22) compared to enoxaparin (0.25). It was noted that only 2 subjects with bleeding event from the enoxaparin/placebo group under concomitant use of CYP3A4 or Pgp inhibitors. A total of 458 rivaroxaban subjects used a CYP3A4 inhibitor at any time during the study. The most common CYP3A4 inhibitors used were cimetidine (n = 118), diltiazem (n = 103), verapamil (n = 101), and amiodarone (n = 52). A total of 128 rivaroxaban subjects used a Pgp inhibitor at any time during the study. The most common Pgp inhibitor used was verapamil (n = 101).

For concomitant use of CYP3A4 or P-gp inhibitors, the rate ratio in the rivaroxaban group appears also higher for any bleeding (RR=1.41, 95% CI: 0.98 – 2.01) compared to the enoxaparin/placebo group (RR=0.83, 95% CI: 0.52 – 1.34).

For concomitant use of ‘platelet aggregation inhibitors or ASA’, the rivaroxaban group shows rate ratios comparable to the enoxaparin/placebo group for both bleeding endpoints.

The Relative Rate of Post-Tablet Major or Non-major Clinically Relevant Bleeding events per 100 Patient-Weeks with Use versus no Use of Concomitant Medications (Post-Tablet Safety Population)

Co-Medication	Rivaroxaban		Enoxaparin	
	% Patient-time exposed to co-medication	Relative Rate Use vs No use (95% CI)	% Patient-time exposed to co-medication	Relative Rate Use vs No use (95% CI)
NSAIDS	36%	1.28 (0.94 to 1.73)	36%	0.90 (0.63 to 1.28)
OPIOID	39%	2.52 (1.72 to 3.71)	40%	1.31 (0.87 to 1.96)
STATIN	15%	1.52 (1.07 to 2.17)	14%	1.26 (0.81 to 1.95)
NITRATE	3%	1.45 (0.72 to 2.94)	3%	1.71 (0.81 to 3.63)
ANTI-PLATELET	5%	1.11 (0.55 to 2.25)	4%	1.13 (0.47 to 2.75)
,CYP3A4 or P-gp INHIBITOR	5%	1.22 (0.68 to 2.18)	5%	0.25 (0.06 to 1.02)

Source: Table: 14.3.5/11.1, PH-35415 5.3.5.3.4-4784
Note: Time under concomitant drug use or up to 2 days after the last intake of concomitant drug considered time of comedication use.
Note: Relative Rate (Rate Ratio) estimate stratified by time after surgery (Days 1-3, Days 4-7, and after Day 7)

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

The carcinogenicity studies in rat and mouse are ongoing.

7.6.2 Human Reproduction and Pregnancy Data

According to the sponsor, rivaroxaban has not shown any evidence of a primary teratogenic potential, but animal reproduction studies have shown pronounced maternal toxicity (e.g. hemorrhagic complications) with secondary effects on fetal development. Due to the intrinsic risk of bleeding and evidence that rivaroxaban crosses the placenta, and since in rats, rivaroxaban is secreted into breast milk, rivaroxaban is contraindicated in pregnant or nursing women. Pharmacology/Toxicology review is pending.

7.6.3 Pediatrics and Effect on Growth

The safety and effectiveness of rivaroxaban in pediatric patients has not been studied. The RECORD study protocols excluded subjects under the age of 18 years from clinical trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no reports of accidental or intentional overdose in the rivaroxaban clinical study program. Doses of up to 30 mg bid (a total of 60 mg per day) have been studied in Phase 2 studies. In a single-dose Phase 1 escalation study, a ceiling effect with no further increase in average exposure was reached at a supra-therapeutic dose of 50 mg rivaroxaban even when taken with food. This effect is most probably the result of the limited solubility of rivaroxaban.

Overdose following administration of rivaroxaban may lead to hemorrhagic complications due to its pharmacodynamic properties. Administration of activated charcoal up to 8 hours after overdose may reduce the absorption of rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable. There are no specific antidotes available for rivaroxaban.

No potential for drug dependence or drug abuse has been noted for rivaroxaban.

No study has been conducted to evaluate the rebound effect of rivaroxaban treatment. In Phase 3 RECORD studies, during the off-treatment period, there were 17 (0.28%) cardiovascular events in the rivaroxaban group as compared to 14 (0.23%) in the enoxaparin group. Among those patients, 11 (66%) events (4 MI, 3 stroke and 4 cardiovascular death) in the rivaroxaban group and 2 (14%) events (1 cardiovascular death and 1 unexplained death) in the enoxaparin group occurred within 10 days after the last dose of treatment; 7 (41%) events (2 MI, 2 stroke, and 3 CV deaths) in the rivaroxaban group and 1 (7%) events (CV death) in the enoxaparin group occurred within 5 days after the last dose of treatment. There were more ischemic stroke events in the rivaroxaban group (6, 0.10%) than in the enoxaparin group (1, 0.02%) during the off treatment period. The earlier occurrence of cardiovascular events and a higher incidence of ischemic stroke during off-treatment raise concerns of possible rebound effect for rivaroxaban after the treatment is withdrawn.

7.7 Additional Submissions

N/A

8 Postmarketing Experience

According to 6-month Safety Update, since the approval of rivaroxaban (Xarelto®) in Canada on 16 September and in Europe on 30 September 2008, postmarketing surveillance with a data cutoff of 5 December, 2008, has identified 2 spontaneous cases of adverse experiences (both from Germany). These cases are described briefly below. An estimate of the total number of patients treated with rivaroxaban as of 5 December 2008 is not available.

Patient #200828853GPV, was a 70-year-old man with a history of arterial hypertension, type 2 diabetes mellitus, and gonarthrosis, who received 10 mg Xarelto for 9 days after knee total endoprosthesis surgery. The patient was also receiving ibuprofen and ibuhexal. On the 9th day of

treatment, the patient experienced bleeding of the sigmoid colon (hemoglobin went from 9.4 g/dl to 7.2 g/dl), for which he received 2 to 3 units of packed red cells; Xarelto was discontinued. Additionally, the patient experienced an increase in renal parameters (laboratory data not provided), which improved after discontinuation of Xarelto and ibuprofen. An increased GGT was reported and was considered serious, but no relationship assessment is available. The physician considered the bleeding sigmoid colon and the increased renal values to be serious and possibly related to Xarelto and ibuprofen, although the increase in renal laboratory values was also considered possibly related to ibuhexal.

Patient #200829844GPV, was a 66-year-old man who was under treatment with Xarelto (duration of treatment and dose not available) and experienced perianal bleeding; Xarelto was withdrawn and bleeding stopped the next day. Two days later, the patient had a recurrence of perianal bleeding and he was advised to undergo an endoscopic colonoscopy/rectoscopy.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

N/A

9.3 Advisory Committee Meeting

FDA Cardiovascular and Renal Drugs Advisory Committee Meeting was held on March 19, 2009 to discuss NDA 22-406 Xarelto (rivaroxaban) oral tablet 10 mg for the proposed indication. The sponsor presented some results from a recently completed ATLAS ACS TIMI 46 6-month study. ATLAS ACS TIMI 46 was a phase 2, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and efficacy of rivaroxaban from 5 mg to 20 mg daily dose in patients with acute coronary syndromes. Only incomplete liver data from this study have been submitted to the Agency in 6-month safety update. For the question of "Do the available clinical data demonstrate a favorable risk-benefit profile for rivaroxaban in the prophylaxis of VTE in patients undergoing hip or knee replacement surgery?" the Committee voted 15 (yes) to 2 (no). One member voted "no" due to concerns for potential for severe hepatotoxicity and the other had concerns for bleeding and overall benefits of rivaroxaban. During discussion, committee members expressed varying levels of concern about the strength of the signals for hepatotoxicity and the feasibility of long term studies to further elucidate the hepatotoxicty seen with rivaroxaban. There were no objections from the committee members for approval without the data from the on-going "long term" atrial fibrillation studies. However, most members stated that longer term studies in identified populations are needed. In regard to

whether a lower dose than 10 mg should be available for special populations based PK/PD studies, the committee voted 5 (Yes) to 9 (No) (abstain 3). Many committee members expressed that there was not enough data to support a lower dose. While some were persuaded that there might be a loss of efficacy others expressed concerns for safety in these specific patient populations (see Quick Minutes dated 3/24/09).

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/s/

Min Lu
4/2/2009 08:31:13 AM
MEDICAL OFFICER

Kathy Robie-Suh
4/2/2009 09:50:22 AM
MEDICAL OFFICER
Concur.